Biomedicine & Pharmacotherapy 120 (2019) 109439

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Adipose tissue as a possible therapeutic target for polyphenols: A case for *Cyclopia* extracts as anti-obesity nutraceuticals

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ARTICLE INFO

Keywords:
Obesity
Adipose tissue
Cyclopia
Phenolic compounds

ABSTRACT

Obesity is a significant contributor to increased morbidity and premature mortality due to increasing the risk of many chronic metabolic diseases such as type 2 diabetes, cardiovascular disease and certain types of cancer. Lifestyle modifications such as energy restriction and increased physical activity are highly effective first-line treatment strategies used in the management of obesity. However, adherence to these behavioral changes is poor, with an increased reliance on synthetic drugs, which unfortunately are plagued by adverse effects. The identification of new and safer anti-obesity agents is thus of significant interest. In recent years, plants and their phenolic constituents have attracted increased attention due to their health-promoting properties. Amongst these, *Cyclopia*, an endemic South African plant commonly consumed as a herbal tea (honeybush), has been shown to possess modulating properties against oxidative stress, hyperglycemia, and obesity. Likewise, several studies have reported that some of the major phenolic compounds present in *Cyclopia* spp. exhibit anti-obesity effects, particularly by targeting adipose tissue. These phenolic compounds belong to the xanthone, flavonoid and benzophenone classes. The aim of this review is to assess the potential of *Cyclopia* extracts as an anti-obesity nutraceutical as underpinned by *in vitro* and *in vivo* studies and the underlying cellular mechanisms and biological pathways regulated by their phenolic compounds.

1. Introduction

The prevalence of obesity has steadily increased in recent decades, with current estimates reporting that approximately 8.9% of the world's population (641 million individuals) are classified as obese with a body mass index (BMI) $\geq$ 30 kg/m^2 [1]. Obesity is regarded as the largest

Abbreviations: ACAT, acyl coenzyme A: cholesterol acyltransferase; ACCα, acetyl coenzyme A carboxylase alpha; AMPK, 5′ AMP-activated protein kinase; ATP, adenosine triphosphate; BAT, brown adipose tissue; β3-AR, beta-3 adrenergic receptor; BMI, body mass index; C/EBPα, CCAAT/enhancer-binding protein alpha; CPT, carnitine palmitoyltransferase; CD11c$^+$, cluster of differentiation 11c$^+$; Chil3, chitinase-like 3; CPEF, crude polyphenol-enriched fraction; CVD, cardiovascular disease; ER, extended release; FA, fatty acid; FFA, free fatty acids; FASN, fatty acid synthase; FDA, food and drug administration; GLP-1, glucagon-like peptide 1; HCD, high-cholesterol diet; HCl, hydrochloride; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; HFrD, high-fructose diet; HIF-1α, hypoxia-inducible factor-1 alpha; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; hMSCs, human mesenchymal stem cells; HPCCC, high performance counter-current chromatography; HSL, hormone sensitive lipase; 5-HT2c, serotonin receptor; IFN-γ, interferon gamma; IL-1β, interleukin 1 beta; IL-4, interleukin 4; IL-6, interleukin 6; IL-10, interleukin 10; IL-13, interleukin 13; iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate 1; JNK, c-Jun N-terminal kinase; LDL-C, low-density lipoprotein cholesterol; LPL, lipoprotein lipase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MD-2, myeloid differentiation protein 2; MCP-1, monocyte chemoattractant protein 1; mRNA, messenger ribonucleic acid; NF-κB, nuclear factor kappa B; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; ScWAT, subcutaneous white adipose tissue; SR, sustained release; T2D, type 2 diabetes; TCA, tricarboxylic acid; TC, total cholesterol; TLR2, toll-like receptor 2; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha; UCP1, uncoupling protein 1; UCP3, uncoupling protein 3; VLDL-C, very low-density lipoprotein cholesterol; vWAT, visceral white adipose tissue; WAT, white adipose tissue

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https://doi.org/10.1016/j.biopha.2019.109439
Received 21 June 2019; Received in revised form 29 August 2019; Accepted 6 September 2019

modifiable risk factor for chronic diseases such as type 2 diabetes (T2D), cardiovascular diseases (CVD) and certain types of cancers [2,3]. Although historically considered a disease of affluence, obesity rates are rapidly increasing in low-and middle-income countries, thus placing a major burden on already struggling and over-burdened health systems [4–6]. While innate biological mechanisms may predispose to obesity, lifestyle factors, which include the consumption of unhealthy, energy-dense diets and limited physical activity, are arguably the main determinants of the current obesity pandemic [4,7], and the focus of first-line anti-obesity strategies, including calorie-restrictive diet and increased physical exercise. However, adherence to behavioral changes are poor, with an increased reliance on synthetic drugs, which are plagued by adverse effects [8,9]. Thus, the identification of new and safer anti-obesity agents is of significant interest. In recent years, plants and their phenolic compounds have attracted increased attention due to their perceived health-promoting properties. Natural products are usually considered safer and more socially acceptable than conventional drugs, and in the case of food, consumed as part of the diet. Amongst these, extracts of *Cyclopia*, an endemic South African plant commonly consumed as a herbal tea (honeybush), has been shown to possess ameliorative properties against oxidative stress, inflammation, hyperglycemia, and obesity [10–18]. Likewise, a number of studies have reported that major phenolic compounds present in *Cyclopia* spp. exhibit anti-obesity effects [19–24].

This review provides a comprehensive summary of all published *in vitro* and *in vivo* studies that have reported on the ameliorative properties of the major phenolic groups (xanthones, flavonoids and benzophenones) and extracts of *Cyclopia* spp. against obesity. Three databases, PubMed, Scopus and Web of Science, were searched for studies published between January 2000 and March 2019, and reporting on the anti-obesity effects of the major phenolic compounds and extracts of *Cyclopia* in adipocytes. Keywords included *Cyclopia*, xanthone, flavonoid, benzophenone, obesity, and adipose tissue, as well as the corresponding synonyms and associated terms for each word (Table S1).

2. Adipose tissue as a therapeutic target

Obesity is characterized by the excessive expansion of white adipose tissue [25], which occurs by either hyperplasia (increase in adipocyte number) or hypertrophy (increase in adipocyte size) [26]. Adipocyte hyperplasia is considered a mechanism for healthy storage of excess energy as triglycerides and releasing of energy as free fatty acids (FFA) during energy deprivation [27]. Adipocyte hypertrophy is associated with hypoxia, fibrosis, oxidative stress, endoplasmic reticulum stress, insulin resistance and adipocyte dysfunction (Fig. 1) [28]. In addition, adipocyte hypertrophy induces cell death and inflammation due to the infiltration of M1 pro-inflammatory macrophages into adipose tissue [28–31]. Adipocyte dysfunction and inflammation are considered the primary mechanisms linking obesity to metabolic disease [32–35] (Fig. 1). Dysfunctional adipocytes secrete high levels of FFA and pro-inflammatory cytokines into the circulation, inducing insulin resistance and inflammation in peripheral tissues such as the liver, muscle, pancreas, heart and brain (Fig. 1). Similar to adipose tissue, increased levels of FFA and pro-inflammatory cytokines induce the recruitment of immune cells in these tissues and subsequently induce chronic inflammatory responses (Fig. 1) [36]. High levels of FFA and pro-inflammatory cytokines, mainly tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), induce insulin resistance in peripheral tissues such as the muscle and liver by directly inhibiting the insulin receptor substrate 1 (IRS-1) signaling or through the activation of inflammatory kinases that inhibit insulin signaling pathways [34]. Furthermore, increased concentrations of circulatory FFA result in ectopic fat deposition in peripheral tissues and increase the production of toxic lipid metabolites such as ceramides, that increases oxidative stress and metabolic dysfunction (Fig. 1) [34].

Increasing evidence highlight the association between copper homeostasis and lipid metabolism [37], with altered copper bioavailabity shown to predict early atherosclerosis, suggesting that copper bioavailability is a potential biomarker for future cardiovascular risk assessment in obese patients with hepatic steatosis [38]. Copper is an essential element for most living organisms and plays a vital role in numerous cellular and physiological functions [39,40]. In adipocytes, copper is essential for mitochondrial respiration and protection against oxygen radicals, and its deficiency is associated with increased fat deposition and adipocyte hypertrophy, mainly as a result of altered processing of metabolic fuels by adipocytes (Fig. 1) [39]. Hence copper bioavailability may be one of the mechanisms inducing adipocyte dysfunction during obesity.

Alterations in gut microbiota play an important role in the development of obesity, and thus the modulation of gut microbiota and microbiota-host interaction could present a promising therapeutic strategy to prevent obesity and obesity-associated complications [41]. Although the pathological events that link altered gut microbiota to obesity are poorly understood, studies have suggested that obesity is associated with the increased translocation of bacteria and bacterial products such as lipopolysaccharides (LPS) into the bloodstream through enhanced intestinal permeability (“leaky gut syndrome”) caused by reduced tight junction expression [42]. Their absorption triggers inflammation by increasing the infiltration of immune cells in adipose tissue and altering adipocytokine production, thus identifying adipose tissue as one of the major targets of gut microbiota derived metabolites [42]. Intestinal bacteria also produce short-chain fatty acids such as butyrate and phenolic acids such as protocatechuic acid, with anti-inflammatory and anti-lipolytic effects, and the ability to suppress fat storage [43–45]. Targeting adipocyte dysfunction thus presents an ideal strategy to treat obesity and prevent adverse systematic effects and the negative effects of obesity on peripheral tissue.

3. Current and emerging therapeutic strategies for obesity

The first-line of treatment for obese individuals is lifestyle modification, with dietary changes towards calorie restriction, and increased physical exercise as the cornerstone (Table 1) [7]. Pharmacotherapy is prescribed for individuals who are unable to control obesity with lifestyle modifications or as an adjunct in overweight or obese individuals with obesity-related comorbidities [46]. Orlistat (PubChem CID: 3034010), approved since 1999 by the Food and Drug Administration (FDA) for the long-term treatment and management of obesity [8,47], inhibits pancreatic lipase activity and fat absorption in the intestine, promoting fecal fat excretion (Table 1) [48,49]. Unfortunately, Orlistat induces several gastrointestinal side-effects such as oily stools, flatulence, increased defecation, and interferes with nutrient and drug absorption [8,50,51]. Over the last decade new pharmacological drugs, including lorcaserin (PubChem CID: 11658860), phentermine/topiramate (PubChem CID: 9848354), phentermine (PubChem CID: 4771), naltrexone/bupropion (PubChem CID: 11556075) and liraglutide (PubChem CID: 16134956) have been approved by the FDA and are currently used for short-term and long-term obesity treatment (Table 1) [8,47]. These drugs act by suppressing appetite or promoting satiety through activation of the serotonin (5-HT2c) receptor, stimulating the release of noradrenalin, inhibiting dopamine and norepinephrine re-uptake, and stimulating the glucagon-like peptide 1 (GLP-1) receptor (Table 1) [9]. Despite their weight-loss efficacy, adverse effects including headaches, insomnia, cardiovascular complications and psychiatric disorders are associated with weight-loss drugs, to the extent that several anti-obesity drugs, such as sibutramine (PubChem CID: 5210), rimonabant (PubChem CID: 104850) or fenfluramine/phentermine (PubChem CID: 9821243), have been withdrawn from the market [8,9,52,53].

Several new drugs or drug combination therapies are in the pipeline or undergoing clinical phase development and may be approved for obesity treatment in the next few years [52]. These potential drugs

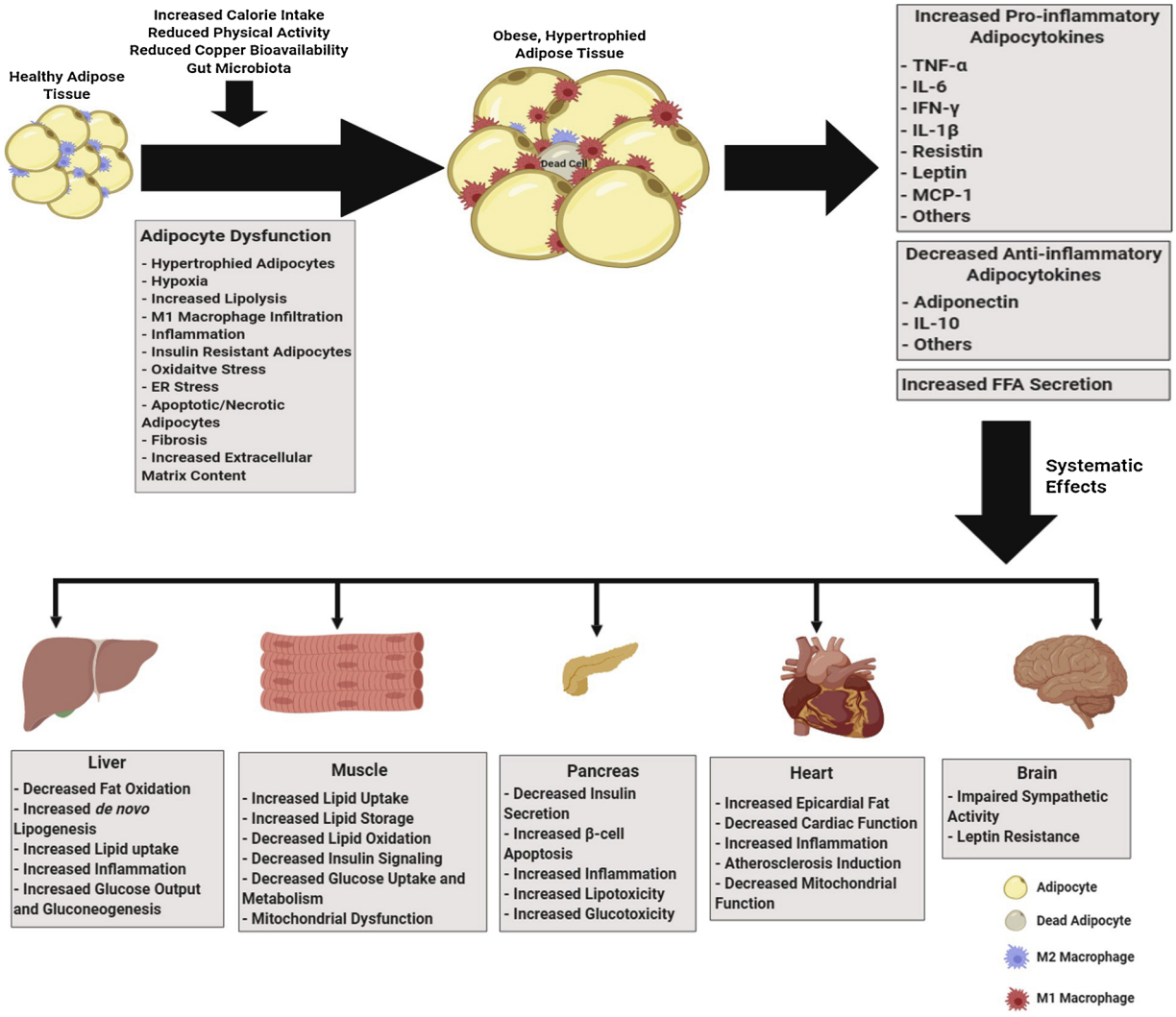

Fig. 1. Adipose tissue dysfunction and systemic effects on peripheral tissues. Adipocytes within healthy normal adipose tissue are infiltrated by M2 macrophages and store excessive energy as triglycerides and release the energy as FFA during energy deprivation. Obesity often leads to adipocyte hypertrophy, which is associated with hypoxia, increased basal levels of lipolysis, oxidative and endoplasmic reticulum stress, fibrosis, adipocyte cell death, recruitment and infiltration of M1 macrophages, chronic inflammation and insulin resistance within adipocytes. This leads to adipose tissue dysfunction which induces excessive secretion of FFA by lipolysis and pro-inflammatory cytokines into the circulation and to key peripheral tissues such as the liver, muscle, pancreas, heart and the brain. High levels of FFA lead to ectopic fat deposition and lipotoxicity in tissues such as liver, pancreas and muscle, while pro-inflammatory cytokines induce systemic low-grade chronic inflammation in the liver, muscle, pancreas, heart and the brain, thus leading to metabolic dysfunction of these tissues and the development of obesity-related diseases.

Figure abbreviations: ER, endoplasmic reticulum; FFA, free fatty acids; IFN-γ, interferon gamma; IL-1β, interleukin 1 beta; IL-6, interleukin 6; IL-10, interleukin 10; MCP-1, monocyte chemoattractant protein 1; TNF-α, tumour necrosis factor alpha.

target the central nervous system, the gastrointestinal tract, as well as various hallmarks of adipocyte dysfunction as described previously [54]. Targeting energy expenditure, particularly adaptive thermogenesis, is now recognized as an attractive alternative approach for obesity treatment [55]. Browning of white adipose tissue (inducing beige adipocytes), or stimulation of thermogenesis in brown adipose tissue have attracted considerable interest as anti-obesity strategies [56,57]. Several compounds that are currently being investigated for their anti-obesity potential, have been reported to induce browning of white adipose tissue or to activate thermogenesis in brown adipose tissue. Beta-3 adrenergic receptor (β3-AR) agonist compounds, such as CL316243 (5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl] amino]propyl]-1,3-benzodioxole-2,2-dicarboxylic acid, disodium salt) (PubChem CID: 5312115) and mirabegron (PubChem CID: 9865528), activate brown adipose tissue and thermogenesis, induce beige adipose tissue in subcutaneous white adipose tissue, and increase energy expenditure and resting metabolic rate in rodents and humans [58–62], demonstrating their potential as anti-obesity agents [62]. Despite the availability of various anti-obesity therapeutics, there is still a lack of effective anti-obesity therapies with negligible side effects. Plant-derived natural products such as phenolic compounds are attracting increasing interest as therapeutic agents due to the perception that they are safer and more cost-effective than synthetic drugs [63]. Phenolic compounds have been shown to modulate the physiological and molecular pathways regulating adiposity, potentially reversing obesity and obesity-related metabolic disease [64,65]. Furthermore, a recent study reported that supplementation of a high-fat/high-sucrose diet with a polyphenol-rich plant extract prevented adipose tissue dysfunction by reducing macrophage recruitment and the accumulation of endotoxins, cholesterol and cholesterol oxides in adipose tissue, thus increasing the lifespan of mice irrespective of their reduced body weight [66]. This suggest that adipose tissue is an important therapeutic target for ameliorating obesity-associated metabolic disorders and increasing the life span of obese subjects.

Table 1
Overview of obesity therapeutic strategies.

Treatment Strategy	Therapy	Mechanism/Activity	References
Lifestyle modification	Diet	Prevents excessive fat accumulation	[7,273,274,275,276,277,278,279]
	Physical activity	Increases metabolic rate	[274,275,276,277,280,281,282,283,284]
Pharmacological drugs	Orlistat[a] (Xenical, Alli)	Reduces fat absorption (pancreatic lipase inhibition)	[8,9,47,285,286,287]
	Lorcaserin[a] (Belviq)	Appetite suppressant and promotes satiety (5-HT2c receptor agonist)	
	Phentermine/topiramate ER[a] (Qsymia)	Appetite suppressant (noradrenalin releaser and anti-convulsant/neurostabilizer)	
	Phentermine HCl[b] (Adipex, Lomaira)	Appetite suppressant (noradrenalin releaser/ sympaticomimetic)	
	Naltrexone SR/buproprion SR[a] (Contrave)	Appetite suppressant (norepinephrine/dopamine re-uptake inhibitor and opioid receptor antagonist)	
	Liraglutide[a] (Saxenda)	Appetite suppressant (GLP-1 receptor agonist)	
Weight-loss surgery/ Bariatric surgery[c]	Gastric sleeve; Adjustable gastric band; Roux-en-Y gastric bypass; Biliopancreatic diversion with duodenal switch	Restricts food intake and reduces nutrient absorption by decreasing stomach size or changing the anatomy of gastrointestinal area; Appetite suppression due to physiological or hormonal changes; Increases energy expenditure	[288,289,290,291]
Adipose physiology	Browning/beiging of white adipose tissue (using phenolic compounds such as resveratrol, naringenin, quercetin)[d]; Inducing thermogenesis (using β3-AR agonists, Exendin-4, Secretin)[d]	Increases energy expenditure	[55,59,62,292,293,294,295,296,297]

Abbreviations: 5-HT2c, serotonin receptor; β3-AR, beta-3 adrenergic receptor; ER, extended release; HCl, hydrochloride; SR, sustained release; GLP-1, glucagon-like peptide 1; FDA, Food and Drug Administration.

[a] Approved by FDA for long-term use.

[b] Approved by FDA only for short term use (≤ 12 weeks) and low dose.

[c] Only recommended for morbidly obese (BMI ≥ 40 kg/m^2).

[d] Compounds currently being investigated or under development.

4. *Cyclopia* spp.

Species from the genus *Cyclopia* Vent. (Family: Fabaceae; Tribe: Podalrieae), also referred to as honeybush, have a long history of use as herbal tea [67]. Of the 23 species described thus far [68], *C. subternata*, *C. genistoides*, *C. intermedia*, *C. maculata*, *C. longifolia* and *C. sessiliflora* are currently used commercially to a greater or lesser extent for tea production [69]. Honeybush tea has gained popularity due to its distinctively sweet flavour, aroma, and caffeine-free status, as well as low tannin content compared to black teas [69,70]. The "fermented" (oxidized) form is mostly produced for herbal tea consumption, while the "unfermented" (green) product with higher polyphenol content and anti-oxidant activity was initially developed as source material for production of nutraceutical extracts [69], but in recent years, a small quantity is also consumed as herbal tea. The global demand for honeybush tea has increased significantly over the last few years, partially attributed to its perceived beneficial health properties. Mounting scientific evidence demonstrates that extracts of *Cyclopia* spp. exhibit potential anti-diabetic [10,15], anti-oxidant [12,18], anti-mutagenic [71], anti-cancer [72], phytoestrogenic [73], anti-osteoclastogenic [74], anti-allergic [75] and anti-inflammatory [18] activities, in *in vitro* and *in vivo* models. Amongst the many phenolic compounds present in *Cyclopia* spp., high quantities of the xanthones, mangiferin (PubChem CID: 5281647) and its isomer, isomangiferin (PubChem CID: 5318597), the flavanone, hesperidin (PubChem CID: 10621), as well as benzophenone glucosides and dihydrochalcone glycosides have been detected [76]. While some of phenolic compounds have beneficial health effects including anti-obesity potential, few studies have reported that extracts of *Cyclopia* spp. exhibit anti-obesity effects [13,14,16,17], prompting investigations into their potential as nutraceuticals for the management of obesity.

4.1. Anti-obesity properties of Cyclopia extracts

Anti-obesity properties of *Cyclopia* was first reported in 3T3-L1 adipocytes, the most commonly used *in vitro* adipocyte cell model [77]. Dudhia et al. [13] demonstrated that an aqueous extract of "fermented" *C. maculata* and aqueous extracts of "unfermented" *C. maculata* and *C. subternata* dose-dependently inhibited adipogenesis, lipid accumulation, triglyceride content and peroxisome proliferator-activated receptor gamma (PPARγ) expression in differentiating 3T3-L1 pre-adipocytes. The aqueous extract of "fermented" *C. maculata* also stimulated lipolysis, and increased hormone sensitive lipase (HSL) and perilipin expression in mature 3T3-L1 adipocyte [14]. Recently, we reported that *C. intermedia* demonstrated anti-obesity potential *in vitro* and *in vivo* [16]. A crude polyphenol-enriched organic fraction of "unfermented" *C. intermedia* decreased lipid content, and increased *Hsl* and uncoupling protein 3 (*Ucp3*) gene expression in 3T3-L1 adipocytes [16]. Furthermore, the extract decreased body weight gain in obese leptin receptor deficient ($Lepr^{db/db}$) mice [16]. To our knowledge, these are the only experiments that have reported on the anti-obesity properties of *Cyclopia* extracts. However, several studies have described the anti-obesity properties of compounds, in particular mangiferin and hesperidin [78–81], that are also present in relative abundance in *Cyclopia* spp. Assessment of their anti-obesity effects based on the existing body of knowledge could guide further studies aimed at enhancing potency and efficacy of *Cyclopia* extracts, underpinning nutraceutical product development.

5. Anti-obesity properties of the major *Cyclopia* polyphenols

5.1. Xanthones

Xanthones are classified into six main groups, the simple xanthones, prenylated xanthones, xanthonolignoids, bisxanthones, miscellaneous xanthones and xanthone glycosides (*C*- or *O*-glycosides) [82]. The two most common *C*-glucosyl xanthones, mangiferin and its structural isomer, isomangiferin, are present in relative high quantities in *Cyclopia* spp. [76], particularly in *C. genistoides* and *C. longifolia* [83]. The glucose moiety of these xanthones is attached to 1,3,6,7-tetrahydroxy-9H-xanthen-9-one *via* a C—C bond at position 2 and 4, respectively. Mangiferin is abundant in plants such as *Mangifera indica* (mango), *Salacia reticulata*, *Anemarrhena asphodeloides* (bunge rhizome), *Mangifera persiciformis* (peach mango), *Curcuma amada* (mango ginger) and *Swertia*

Table 2
Summary of studies reporting on the anti-obesity properties of phenolic compounds of *Cyclopia* spp. and the mechanism of their biological activity using *in vitro* adipocyte models.

Compound	Experimental Model	Dose and Treatment Period	Experimental Outcomes and Proposed Mechanism	References
Mangiferin	Rat epididymal derived adipocytes	100 mg/l for 18 h	Increased lipolysis	[84]
	Differentiating hMSCs pre-adipocytes	20 and 40 μM from day 0 to day 10 of differentiation	Inhibited adipocyte differentiation and lipid accumulation by decreasing *Pparγ*, *Lpl*, *aP2*, *Tnf-α* and *resistin* gene expression; Increased adiponectin expression	[80]
	Hypoxia induced insulin-resistant 3T3-L1 adipocytes	0.1, 1, and 10 μM for 8 h	Decreased lipolysis; Increased protein expression of AMPK phosphorylation and upregulated *adiponectin* gene expression; Inhibited NF-κB activation, decreased HIF-1α protein expression; Reduced *Il-6*, *Mcp-1*, *resistin*, *leptin*, *Vegf* and *Tnf-α* gene expression, and decreased IL-6 and TNF-α secretion; Improved insulin signaling and increased insulin-induced GLUT4 translocation	[85]
Hesperidin	Differentiating 3T3-L1 pre-adipocytes	5, 10 and 20 μM for 6 days during differentiation	Decreased lipid accumulation and TG content by decreasing *Pparγ*, *C/ebpα* and *Fabp4* gene expression; Reduced ROS production	[81]
	Differentiating hMSCs pre-adipocytes; Differentiated hMSCs adipocytes (ADMSCs)	1, 10 or 25 μM from day 0 to day 8 of differentiation; Mature adipocytes for 48 h	Reduced TG content and inhibited adipogenic and lipogenic gene expression (*C/ebpβ*, *Srebp1c*, *Fasn* and *Plin1*); Increased lipolysis by increasing *Atgl* gene expression	[130]
Hesperidin, naringenin and luteolin	Differentiating 3T3-L1 pre-adipocytes	1, 10 or 25 μM for 8 days during differentiation	Reduced lipid accumulation and decreased *C/ebpβ*, *Srebp1c*, *Acc* and *Lpl* gene expression	[131]
	Differentiating 3T3-L1 pre-adipocytes	10, 50, 100 μM from day 0 to day 8 during differentiation; 10, 50, 100 μM from day 5 to day 13 of differentiation; 10, 50, 100 μM from day 8 to day 16 of differentiation	Decreased lipid accumulation; Reduced *Scd1* and *Plin1* gene expression	[298]
Hesperetin	Differentiating hMSCs pre-adipocytes; Differentiated hMSCs adipocytes (ADMSCs)	5, 10 and 20 μM on day 0 of differentiation; 5, 10 and 20 μM from day 3 to day 10 during differentiation	Stimulated lipolysis; Inhibited adipocyte differentiation by reducing TG content, and lipid accumulation; Reduced PPARγ and C/EBPα protein expression; Inhibited *resistin*, *aP2*, *Lpl*, *Pparγ* and *Tnf-α* gene expression; Increased *adiponectin*, *Bcl*, *Bax*, and *p21* gene expression	[129]
	Differentiating 3T3-L1 pre-adipocytes	6.25, 12.5 and 25 μM for 8 days during differentiation	Inhibited lipid accumulation by decreasing PPARγ, C/EBPα, aP2, SREBP1c, FASN, DGAT1, LPAATΘ, Lipin1 and G6PDH gene and protein expression; Reduced ROS production by decreasing NOX4 protein expression and increasing SOD2, GPx, and GR gene and protein expression	[128]
Hesperetin and naringenin	Differentiating 3T3-L1 pre-adipocytes; Differentiated 3T3-L1 adipocytes	5, 10 and 30 mg/ml from day 0 to day 10 during differentiation; 80 μM for 48 h	Decreased lipid accumulation and *Pparγ2* gene expression; Increased gene transcription of *adiponectin*	[127,299]
	TNF-α-induced 3T3-L1 adipocytes; Mouse primary adipocytes	Pretreated at 100 μM for 30 min and stimulated with 10 ng/ml TNF-α; 50 ng/ml (primary adipocytes) for 24 h	Suppressed FFA secretion; Increased *Plin1* and *Pde3b* gene expression; Inhibited NF-κB and ERK pathways; Reduced *Il-6* gene expression	[148]
Naringenin	Differentiating 3T3-L1 pre-adipocytes; NIH-3T3 adipocytes; Hypertrophied 3T3-L1 adipocytes co-cultured with RAW 264 macrophages	25, 50 and 100 μM from day 0 to day 8 during differentiation; 25, 50 and 100 μM for 24 h in differentiated adipocytes; 50, 100 and 200 μM in co-cultured adipocytes and macrophages	Increased gene expression of *adiponectin* and *AdipoR2*; Increased adiponectin secretion; Increased transcriptional *Pparγ* activity; Increased expression of mitochondrial energy metabolism genes; Decreased MCP-1, TNF-α and NO secretion levels	[149,150,300]
	Differentiating 3T3-L1 pre-adipocytes; Differentiated 3T3-L1 adipocytes; Human subcutaneous adipocytes	6, 12, 25 and 50 μg/ml for 8 days during differentiation; 25 μg/ml during 0, 24, 48, 72, 96, and 120 h of differentiation; 12, 25 and 50 μg/ml for 1.5, 2, 5, 24, 48 and 72 h; 20 and 40 μM for 9 days during differentiation	Decreased adipocyte differentiation and lipid accumulation; Decreased aP2, PPARγ and STAT5A protein expression; Reduced insulin-stimulated glucose uptake and the protein expression of IRS-1 phosphorylation	[147,301]
	3T3-L1 pre-adipocytes; Differentiating 3T3-L1 pre-adipocytes; Differentiated 3T3-L1 adipocytes; TNF-α stimulated 3T3-L1 adipocytes; 3T3-L1 adipocytes co-cultured with RAW 264 macrophages	1–100 μM for 3-6 h; 1–100 μM for 7 days during differentiation; Pre-treated at 100 μM for 30 min and stimulated with 10 ng/ml TNF-α for 5-10 min, or 3 and 6 h; Pre-treated at 10 and 50 μM for 30 min and co-cultured with RAW264 cells for 3 h	Decreased TLR2 and MCP-1 gene and protein expression; Reduced TLR2 and MCP-1 secretion; Inhibited NF-κB and JNK pathways	[151,152]

(*continued on next page*)

Table 2 (*continued*)

Compound	Experimental Model	Dose and Treatment Period	Experimental Outcomes and Proposed Mechanism	References
	Rat adipocytes isolated from epididymal adipose tissue	62.5, 125, 250 and 500 μM for 90 min or 4 h	Decreased basal and insulin-stimulated lipogenesis; Reduced epinephrine-stimulated lipolysis	[302]
	Human white adipocyte cultures (hADSC); Abdominal subcutaneous adipose tissue	8 μM for 7 to 14 days	Promoted thermogenic gene expression including *Ucp1*, *Atgl*, *Cpt-1β*, *Glut4*, *Chrebp*, *Chrebpβ*, *adiponectin*, *Pgc1α* and *Pgc1β*; Increased UCP1, GLUT4, ChREBP, PGC1α and PGC-1β protein expression; Increased protein expression of AMPK phosphorylation; Increased energy expenditure by improving OCR	[153]
Luteolin	Differentiated 3T3-L1 adipocytes	20 μM for 24 h	Decreased *Il-6* and *Mcp-1* gene expression; Increased *Pparγ* transcriptional activity; Increased *adiponectin* and *leptin* gene expression	[195]
	Hypertrophied 3T3-L1 adipocytes co-cultured with RAW 264 macrophages; 3T3-L1 adipocytes stimulated with TNF-α, LPS and IFN-γ combination	Pre-treated at 2.5, 5 and 10 μM for one h and stimulated with TNF-α + LPS + IFN-γ (10 ng/ml) for 6 or 24 h; 3T3 L1 adipocytes pre-treated at 2.5, 5 and 10 μM for 24 h and stimulated with TNF-α (10 ng/ml) for 30 min; 0.1, 1, 5, 10 and 20 μM for 24 h	Decreased MCP-1, TNF-α, NO and IL-6 secretion; Reduced gene expression of *iNos*, *Cox2*, *Il-6*, *Mcp-1* and *resistin*; Decreased protein expression of iNOS, NF-κB activation, ERK phosphorylation, JNK phosphorylation and p38 MAPK phosphorylation	[201,202]
	Differentiating 3T3-L1 pre-adipocytes	1, 5, 10, 20, 25, 50 and 75 μM for 2, 4, 7, 8 and 9 days during differentiation	Reduced lipid accumulation and TG content; Decreased *aP2*, *Pparγ*, *C/ebpα*, *Srebp1c*, *Acc1*, *Fasn*, *Hsl* and *Lpl* gene expression; Reduced PPARγ, C/EBPα and FASN protein expression	[196,197,198,199]
	Differentiating 3T3-L1 pre-adipocytes treated simultaneously with rosiglitazone; Differentiated 3T3-L1 adipocytes treated simultaneously with rosiglitazone	5, 10, or 20 μM and 1 μM rosiglitazone for 3 days, whereafter cells maintained until day 8 of differentiation; 10 and 20 μM and 1 μM rosiglitazone for 24 h	Decreased lipid accumulation; Reduced *Pparγ*, *Lpl* and *C/ebpα* gene expression	[200]
	Differentiated 3T3-L1 adipocytes stimulated with macrophage-conditioned media	Pre-treated at 10 μM for 0.5 h and stimulated with macrophage-conditioned medium for 0.5 h	Increased glucose consumption; Increased protein expression of AMPK phosphorylation and SIRT1; Increased *adiponectin* gene expression; Suppressed the protein expression of NF-κB p65 phosphorylation; Decreased *Tnf-α*, *Il-6* and *Mcp-1* gene expression	[203]
	Differentiating primary BAT and ScWAT pre-adipocytes	Pre-treated with 20 μM Compound C for 2 h and treated with 100 nM (luteolin) or 2 mM AICAR for 24 h	Increased UCP1, PRDM16, PGC1α, PPARα, CIDEA, ELOVL3, SIRT1, TMEM26, CD137 and CITED1 gene and protein expression; Activated AMPKα/PGC1α signaling	[204]
3-β-D-glucopyranosyliriflophenone	Differentiating 3T3-L1 pre-adipocytes	10 and 30 μM for 14 days during differentiation	Decreased TG content and FFA accumulation; Reduced *Acc*, *Hsl*, *Fasn* and *Srebp1c* gene expression; Increased *Ampk* gene expression	[235,236,237]
3-β-D-glucopyranosylmaclurin	Differentiating 3T3-L1 pre-adipocytes	30 μM for 14 days during differentiation	Decreased lipid accumulation, TG content and FFA accumulation; Decreased *Acc*, *Hsl*, *Fasn* and *Srebp1c* gene expression; Increased *Ampk* gene expression	[235]

Abbreviations: ACC, acetyl coenzyme A carboxylase; ADIPOR2, adiponectin receptor 2; ADMSCs, adipose-derived mesenchymal stem cells; AICAR, 5-Aminoimidazole-4-carboxamide ribonucleotide; AMPK, 5′ AMP-activated protein kinase; aP2, adipocyte protein 2; ATGL, adipose triglyceride lipase; BAT, brown adipose tissue; BAX, BCL2-associated X protein; BCL, B-cell lymphoma 2; C/EBPα, CCAAT/enhancer-binding protein alpha; C/EBPβ, CCAAT/enhancer-binding protein beta; CD137, tumor necrosis factor receptor superfamily member 9; CIDEA, cell death-inducing DNA fragmentation factor α-like effector A; CITED1, Cbp/p300-interacting transactivator 1; ChREBP, carbohydrate-responsive element-binding protein; ChREBPβ, carbohydrate-responsive element-binding protein beta; COX2, cyclooxygenase-2; CPT-1β, carnitine palmitoyltransferase 1 beta; DGAT1, diglyceride acyltransferase 1; ELOVL3, ELOVL fatty acid elongase 3; ERK, extracellular-signal-regulated kinase; FABP4, fatty acid binding protein 4; FASN, fatty acid synthase; FFA, free fatty acids; G6PDH, glucose-6-phosphate dehydrogenase; GLUT4, glucose transporter 4; GPx, glutathione peroxidase; GR, glutathione reductase; HIF-1α, hypoxia-inducible factor 1-alpha, hADSC, human adipose-derived stem cells; hMSCs, human mesenchymal stem cells; HSL, hormone-sensitive lipase; IFN-γ, interferon gamma; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate 1; JNK, c-Jun N-terminal kinase; LPL, lipoprotein lipase; LPAATΘ, lysophosphatidic acid acyltransferase; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein 1; NF-κB, nuclear factor kappa B; NO, nitric oxide; NOX4, NADPH oxidase 4; OCR, oxygen consumption rate; p21, cyclin-dependent kinase inhibitor 1; p38 MAPK, p38 mitogen-activated protein kinase; p65, nuclear factor NF-kappa-B p65 subunit; PDE3B, phosphodiesterase 3B; PGC1α,

peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PGC1β, peroxisome proliferator-activated receptor gamma coactivator 1 beta; PLIN1, perilipin 1; PPARα, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; PRDM16, PR domain containing 16; ROS, reactive oxygen species; SCD1, stearoyl-CoA desaturase-1; ScWAT, subcutaneous white adipose tissue; SIRT1, sirtuin-1; SOD2, superoxide dismutase 2; SREBP1c, sterol regulatory element-binding protein 1c; STAT5A, signal transducer and activator of transcription 5A; TG, triglycerides; TLR2, toll-like receptor 2; TMEM26, transmembrane protein 26; TNF-α, tumour necrosis factor alpha; UCP1, uncoupling protein 1; VEGF, vascular endothelial growth factor.

ciliata [19,20]. Various *in vitro* and *in vivo* studies have reported on the anti-obesity effects of mangiferin (Tables 2 and 3). Mangiferin stimulated lipolysis in rat epididymal derived adipocytes [84], inhibited adipogenesis and lipid accumulation in human mesenchymal stem cells (hMSCs) [80] and ameliorated inflammation and insulin resistance in hypoxic 3T3-L1 adipocytes (Table 2) [85]. *In vivo*, mangiferin decreased body weight and visceral adiposity, and improved hyperlipidemia by decreasing circulating levels of triglycerides, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and FFA in high-fat diet (HFD) and high-fructose diet (HFrD) fed rodents (Table 3) [78,86–90]. Visceral adiposity positively correlates with LDL-C levels and cholesterol synthesis [91,92], suggesting that mangiferin targets visceral adipose tissue to decrease FFA secretion and transport to the liver, subsequently ameliorating hyperlipidemia by reducing the production of LDL-C in the liver and its circulating levels, in diet-induced obese models.

Mangiferin is also reported to stimulate adiponectin secretion in HFD fed mice (Table 3) [87,93]. Adiponectin is an adipocyte-specific hormone with insulin-sensitizing properties that is decreased during obesity and hyperlipidemia [94–100]. Mangiferin also induces energy expenditure by increasing mitochondrial oxidative capacity and thermogenesis, lowers endoplasmic reticulum stress in perivascular adipose tissue of HFD fed ICR mice, and suppresses hepatic and systematic inflammation in HFD fed mice [87,90,93,101–103]. Furthermore, high-throughput metabolomic approaches (Table 3) suggest that mangiferin ameliorates hyperlipidemia by regulating metabolic pathways such as glycolysis, tricarboxylic acid (TCA) cycle, and lipid metabolism in HFD fed rodents [104,105]. Our literature search identified only one human study reporting on the anti-obesity properties of mangiferin (Table 4). In this study, treatment of overweight and hyperlipidemic patients with mangiferin (150 mg/kg daily for 12 weeks) decreased triglyceride and FFA levels, and increased high-density lipoprotein cholesterol (HDL-C) levels and lipoprotein lipase (LPL) activity [106]. In the gut, intestinal bacteria transform mangiferin to an active aglycone metabolite, norathyriol (PubChem CID: 5281656), by cleavage of the *C*-glucosyl bond [107]. Norathyriol has hypoglycemic [108–110], anti-inflammatory [111] and anti-obesity [112,113] properties. In HFD-fed mice, norathyriol reversed obesity and insulin resistance by inhibiting protein tyrosine phosphatase 1 B (PTP1B) activity [112], while suppressing triglyceride accumulation and improving hepatic lipid metabolism through modulating the sirtuin-1/5′ AMP-activated protein kinase/sterol regulatory element-binding protein 1c (SIRT-1/AMPK/SREBP1c) signaling in HepG2 human liver cells [113]. Our literature search could not identify any studies reporting on the anti-obesity properties of isomangiferin in both *in vitro* and *in vivo* models of obesity, although exposure of C2C12 myocytes to isomangiferin enhanced glucose uptake similar to mangiferin [11], demonstrating its anti-diabetic potential.

5.2. Flavonoids

Flavonoids comprise a class of polyphenols that are ubiquitous in plants and the human diet [114–116]. Flavonoids are classified into sub-classes, with glycosides belonging to the flavanone (hesperidin, (2*S*)-5-[α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyloxy] naringenin and neoponcirin), flavone (scolymoside and vicenin-2) and dihydrochalcone (phloretin-3′,5′-di-*C*-β-D-glucoside and 3-hydroxyphloretin-3′,5′-di-*C*-hexoside) classes detected in *Cyclopia* extracts [117–125]. Several of the flavonoids or their aglycones have been reported to exert anti-obesity properties, as discussed below.

5.2.1. Flavanones

Hesperidin (hesperetin-7-*O*-rutinoside) is one of the major polyphenols detected in *Cyclopia* extracts [76]. In contrast, hesperetin (4′-methoxy-3′,5,7-trihydroxyflavanone) (PubChem CID: 72281), the aglycone of hesperidin, has been detected in low quantities in *Cyclopia* extracts. However, hydrolysis of hesperidin in the gut by microbiota

Table 3
Summary of studies reporting on the effects of phenolic compounds of *Cyclopia* spp. on obesity and associated comorbidities, and the mechanism of their biological activity *in vivo* in animal models of obesity.

Compound	Experimental Model	Dose and Treatment Period	Experimental Outcomes and Proposed Mechanism	References
Mangiferin	High-fat diet fed male golden Syrian hamsters	50 and 150 mg/kg BW daily for 8 weeks	Decreased BW and reduced eWAT, pWAT and liver weights; Reduced TG and FFA levels in serum, liver and muscle; Increased hepatic and muscle *Ppara*, *Cd36*, *Cpt-1* and *Lpl* gene expression; Decreased hepatic *Srebp1c*, *Acc*, *Dgat2* and *Mtp* gene expression; Regulated metabolic pathways involved in glycolysis, TCA cycle and lipid metabolism	[78,104]
	High-fat diet fed male hyperlipidemic Wistar and Sprague Dawley rats	50, 100, 150 and 300 mg/kg BW daily for 6 or 13 weeks	Reduced eWAT and hepatic fat accumulation; Decreased plasma, serum and hepatic TG, TC, LDL-C and FFA levels; Increased plasma, serum and hepatic HDL-C and β-hydroxybutyrate levels; Increased fecal TG and TC content; Increased phosphorylation of AMPK and ACC in the liver; Upregulated the hepatic expression of CD36 and CPT-1; Decreased DGAT2 expression in liver; Regulated metabolic pathways involved in TCA cycle and glycerophospholipid metabolism	[89,105]
	High-fat and high-fructose diet fed male Wistar rats induced with STZ	20 and 40 mg/kg BW daily for 28 days or 6 weeks	Decreased serum and hepatic TG, TC, LDL-C, TNF-α and Hs-CRP levels; Reduced serum and hepatic MDA content; Increased serum HDL-C and adiponectin levels	[93,303]
	High-fat diet fed male C57BL6/J mice	0.25% and 0.5% supplemented diet (g/g food) *ad libitum* for 16 or 18 weeks; 400 mg/kg BW *ad libitum* for 16 weeks; 5 and 20 mg/kg diet *ad libitum* for 12 weeks	Decreased BW gain and reduced fat and lean mass; Decreased liver weight and hepatic steatosis; Decreased plasma TG, TC and LDL-C levels, and increased plasma HDL-C levels; Decreased plasma IL-6 and TNF-α levels, and increased plasma IL-10 levels; Improved glucose intolerance and insulin sensitivity; Increased plasma adiponectin levels; Increased thermogenesis and energy expenditure; Induced muscle mitochondrial biogenesis; Increased hepatic and muscle protein and gene expression of mitochondrial bioenergetics genes including DHTKD1, COX6B1, *Idh*, *α-kgdh*, *Sdhβ*, *CoxI*, *Cyt-c*, *CoxIV*, *Atp5g1*, *Tfam*, *Nrf*, *Errα*, *Pgc1α* and *Pgc1β*; Decreased hepatic ACC and SCD1 protein expression	[87,88,10-1,103]
	Fructose diet fed spontaneously hypertensive and Wistar-Kyoto male rats	5 and 15 mg/kg BW daily for 7 weeks	Decreased plasma NEFA levels; Reduced hepatic TG and lipid accumulation; Decreased adipose tissue insulin resistance index; Reduced hepatic DGAT2 protein expression and reduced intracellular CD36 distribution in skeletal muscle	[304,305]
	High-fat diet fed male Kunming mice	15, 30 and 60 mg/kg BW daily for 12 weeks	Decreased BW; Reduced serum and hepatic TG and TC levels; Suppressed inflammation by inhibiting NF-κB and JNK pathway; Regulated autophagy and lipogenesis *via* AMPK/mTOR signaling	[90]
	Obese and lean phenotype female Zucker rats	15 mg/kg BW daily for 8 weeks	Reduced BW; Decreased plasma TC, LDL-C and FGF21 levels; Reduced plasma IFN-γ, IL-1β and IL-6 levels; Increased plasma HDL-C levels and muscle oxidative capacity	[86]
	High-fat diet fed ICR male mice	50 mg/kg BW daily for 2 weeks	Suppressed ER stress, oxidative stress and inflammation in pvWAT; Increased protein expression of LKB1, AMPK and ACC phosphorylation in pvWAT	[102]
Hesperidin	C57BL/KsJ- *db/db* (Lepr$^{db/db}$) male mice	200 mg/kg diet for 5 weeks	Decreased plasma and hepatic FFA, TG and TC levels; Reduced hepatic β-oxidation; Decreased hepatic FASN, CPT, ACAT and HMG-CoA reductase activities	[132]
	High-cholesterol diet fed male Wistar rats	0.08% supplemented diet (g/g food) for 12 weeks	Decreased adipose tissue weight; Reduced liver weight and hepatic steatosis; Reduced serum TC, lathosterol, campesterol, β-sitosterol and RBP4 levels	[79]
	High-fat diet fed male *Ldlr*$^{-/-}$ C57BL/6 JNju mice	100 and 200 mg/kg BW daily for 12 weeks	Decreased BW gain and HOMA-IR index; Decreased serum and hepatic TC, TG, LDL-C, ox-LDL, SOD, GPx, IL-6 and TNF-α levels; Reduced hepatic steatosis, decreased hepatic ACCα, FASN, *Il-6* and *Tnf-α* protein and gene expression and increased ABCG8 hepatic protein expression; Increased hepatic SOD and GPx activity; Reduced atherosclerotic lesion formation, increased ABCA1 and ABCG1 expression in aorta and decreased T*nf-α* gene expression in aorta	[133]
	High-fat diet fed white male albino rats induced with STZ	50 mg/kg BW daily for 4 weeks	Increased adiponectin gene expression and decreased *Il-6* gene expression in adipose tissue; Decreased serum glucose, LPO, NO, TNF-α and IL-6 levels, and increased serum insulin and GSH levels; Decreased HbA1c and HOMA-IR index; Decreased hepatic LPO and NO levels and increased hepatic GSH content; Increased hepatic CAT, GPx, GR and SOD activities	[306,307]
	Young (6 months) and old (27–29 months) male C57BL/6 mice on normal, low-fat rodent diet	0.5% supplemented diet (g/g food) for 4 weeks	Reduced age-induced pvWAT mediated aortic stiffness and AGE accumulation; Reversed pvWAT mediated aortic inflammation and oxidative stress	[308]
	Caenorhaditis elegans (High-fat) and (daf-2 mutant) worms	50 and 100 μM for 46 h on standard nematode growth medium plates	Reduced fat accumulation and the ratio of oleic acid/stearic acid; Decreased expression of lipid metabolism genes	[137]
	High-fat and high-sucrose diet fed male Wistar rats	100 mg/kg BW daily for 8 weeks	Improved blood lipid profile; Reduced hepatic lipid accumulation and prevented liver steatosis; Reduced adipose tissue (iWAT, rWAT, eWAT and mWAT) weights; Increased UCP1 and CIDEA accumulation in rWAT	[309,310]
	Fructose-enriched diet fed male Wistar albino rats	5 mg/kg BW daily for 4 weeks	Decreased serum TG, TC, MDA, NO and TNF-α levels; Increased GSH serum levels; Reduced liver steatosis	[311]
Hesperetin	Orotic acid diet fed male Sprague-Dawley rats	1% supplemented diet (g/g food) for 10 days	Decreased hepatic TG and TC content; Reduced hepatic microsomal PAP, DGAT, G6PDH and malic enzyme activities; Reduced serum phospholipid levels	[312]
	High-cholesterol diet fed male Sprague–Dawley rats	0.02% supplemented diet (0.066 mmol/100 g diet) for 5 or 6 weeks	Decreased plasma TC and TG concentrations, and plasma atherogenic index; Reduced hepatic HMG-CoA reductase and ACAT activities; Decreased hepatic TC content	[313,314]
	High-fat diet fed male golden Syrian hamsters			[315]

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Table 3 (*continued*)

Compound	Experimental Model	Dose and Treatment Period	Experimental Outcomes and Proposed Mechanism	References
		0.02% supplemented diet (0.066 mmol/100 g diet) for 12 weeks	Decreased plasma Apo B and PON levels; Reduced hepatic cholesterol, TG and H_2O_2 levels; Increased hepatic CAT and GR levels; Reduced hepatic HMG-CoA reductase and ACAT activities	
	Chow diet fed male Wistar rats	0.5% supplemented diet (0.0164 mmol/g diet) for 3 weeks	Decreased abdominal adipose tissue and eWAT weight; Increased fecal starch excretion and cecal pool of short-chain fatty acids	[135]
	High-fat diet fed male C57BL/6 JOlaHsd mice	0.33% supplemented diet (0.01 mmol/g diet) for 12 weeks	Reduced BW gain, mWAT weight and total food efficiency ratio; Reduced serum leptin levels and eWAT leptin expression; Decreased hepatic *Cyp2b9* gene expression	[134]
	High-fat diet fed male Apo-E KO mice	0.1% supplemented diet (g/g food) for 12 weeks	Reduced plasma cholesterol levels; Decreased adipose deposition; Reduced macrophage infiltration in the endothelial tissue	[316]
Hesperetin and naringenin	High-fat diet fed ICR male mice	100 mg/kg BW twice a week for 14 weeks	Reduced abdominal adipose tissue; Decreased plasma TG, TC and LDL-C levels; Reduced TC levels in the liver; Increased hepatic *Ucp2*, *Ucp3*, *Acox1*, *Cpt-1* and *Pparα* gene expression	[127]
Naringenin	Normal diet fed ICR mice	1% supplemented diet for 21 days	Decreased serum TG, TC, FFA and phospholipid levels; Increased enzymatic activity and expression of hepatic enzymes involved in fatty acid oxidation	[167]
	High-fat, high-cholesterol and Low-fat, high-cholesterol diet fed male *Ldlr*$^{-/-}$ C57BL/6 J mice	3% supplemented diet (wt/wt diet) for 12 and 24 weeks	Reduced BW and increased energy expenditure by increasing the RER; Reduced eWAT size and adiposity index and decreased vWAT and ScWAT fat volume; Improved glucose homeostasis and enhanced insulin sensitivity by reducing plasma glucose and insulin levels; Reduced *Tnf-α*, *Il-6*, *Il-1β*, *Ccl2*, *Ccl3*, *F4/80* and *Saa1/2* gene expression in eWAT, iWAT and BAT; Decreased plasma and hepatic TC, TG, VLDL-C, LDL-C, leptin and SAA levels and reduced TG and apo B100 secretion; Decreased hepatic FA synthesis and increased FA oxidation in the liver; Reduced hepatic *Srebp1c*, *Tnf-α*, *Il-1β*, *Ccl2*, *Ccl3*, *F4/80* and *Saa1/2* gene expression; Increased hepatic *Cyp7a1*, *Fgf21*, *Cpt-1*, *Srebf2*, *Hmgcr*, *Pgc1α*, and *Acox* gene expression; Decreased muscle TG content; Prevented atherosclerosis by reducing aortic lipid accumulation, TC and TG levels and decreasing *Tnf-α*, *Il-1β* and *Ccl2* gene expression in aorta	[22,162]
	Chow diet fed and low-fat chow diet fed *Ldlr*$^{-/-}$ male C57BL/6 J mice	3% supplemented diet (wt/wt) for 8 weeks	Decreased BW and reduced eWAT and iWAT weights; Reduced energy expenditure; Reduced plasma TG and TC levels and increased plasma β-hydroxybutyrate levels; Decreased blood glucose and plasma insulin levels; Enhanced hepatic fatty acid oxidation by increasing *Pgc1α* and *Pnpla2* gene expression	[161]
	High-fat diet fed male C57BL/6 J wild-type and *Ldlr*$^{-/-}$ mice	1% and 3% supplemented diet (wt/wt diet) for 4 and 30 weeks, or 6 months	Decreased BW gain and adiposity index and reduced hypertrophy in eWAT; Increased energy expenditure and reduced lipid content in iBAT; Decreased plasma and hepatic TG, CE, TC, leptin and insulin levels, reduced HOMA-IR index, and increased plasma LPL activity; Reduced hepatic TG, FA, CE and TC synthesis; Reduced hepatic lipid content and steatosis, and decreased TG and Apo B100 secretion; Increased hepatic FA oxidation and mtDNA content; Increased hepatic *Pgc1α*, *Cpt-1α* and *Aco* gene expression; Decreased hepatic and muscle gene expression of *Srebp1c*; Reduced TG and TC mass in intestine and aorta	[173,174]
	High-cholesterol diet fed male Wistar and Sprague-Dawley rats	50 mg/kg BW daily for 3 months; 0.02% supplemented diet (0.073 mmol/100 g diet) for 5 or 6 weeks	Decreased BW gain; Reduced plasma, hepatic and cardiac TC, TG, FFA, LDL-C and phospholipid levels; Increased plasma HDL-C levels and reduced plasma TBARS levels; Reduced hepatic and cardiac TBARS, LOOH and ROS levels; Reduced hepatic and cardiac protein carbonyl content; Increased hepatic GSH, SOD, CAT and GPx levels; Decreased hepatic and cardiac *Tnf-α*, *Il-6*, *Il-1β*, *iNos*, *Emr1* and *Nf-κb* gene expression; Decreased hepatic fibrosis and reduced hepatic DNA fragmentation; Reduced hepatic HMG-CoA reductase and ACAT activities; Increased mitochondrial enzyme activities in the heart	[166,170,-171,175]
	High-sucrose diet fed male Long-Evans hooded rats	0.003%, 0.006%, and 0.012% supplemented diet (g/100 g diet) for 6 weeks	Decreased parametrial adipose tissue and TG content in parametrial adipose tissue; Decreased liver weight; Increased hepatic PPARα, UCP2 and CPT-1 protein expression; Decreased plasma and hepatic TG, TC and free cholesterol levels	[165]
	High-fat diet fed male C57B6 J/L mice and Wistar albino rats	50 and 100 mg/kg daily for 28 days; 10 mg/kg BW daily for 4 weeks; 100 mg/kg daily for 1, 7 and 14 days; 1% supplemented diet (g/g diet) for 16 weeks	Reduced BW, eWAT weight, and adiposity index; Decreased *Tlr2*, *Tnf-α*, *Mcp-1* and *Mac-2* gene expression in eWAT, reduced protein expression of MCP-1 and JNK phosphorylation in eWAT and reduced Mac-2 positive cells in eWAT; Increased *Ucp1* and *Cpt-1* gene expression in BAT; Reduced serum and plasma TG, TC, LDL-C, insulin and glucose levels; Reduced serum TBARS levels; Increased SOD and CAT levels in erythrocyte lysates; Decreased hepatic *Fasn* gene expression; Increased hepatic *Cpt-1*, *Pparγ1* and *Pparα* gene expression	[151,152,-154,155,-156,163]
	Caenorhaditis elegans	50 μM for 46 h on standard nematode growth medium plates containing Nile Red dye	Decreased fat accumulation	[317]
	High-fat diet fed male C57BL6/J wild-type and *Fgf21*$^{-/-}$ mice; Low-fat diet fed male Lep$^{ob/ob}$ mice	3% supplemented diet (wt/wt diet) for 4, 8 and 16 weeks	Decreased BW and reduced vWAT and ScWAT volume; Reduced number of adipocytes and adipocyte hypertrophy in eWAT; Increased gene expression of *Pgc1α*, *Cpt-1α*, *Lepr*, *Ucp1*, *Atgl*, *Hsl*, *Pparα* and *Chrebp* in eWAT; Decreased hepatic and muscle TG content; Reduced plasma TG, leptin, insulin, glucose and TNF-α levels; Improved glucose tolerance and inhibited insulin resistance; Decreased hepatic *Srebp1c*, *Acc1*, *Acc2* and *Scd1* gene expression; Increased hepatic *Pgc1α*, *Cpt-1α* and *Lepr* gene expression	[157]

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Table 3 (*continued*)

Compound	Experimental Model	Dose and Treatment Period	Experimental Outcomes and Proposed Mechanism	References
	High-fat diet fed male Wistar albino and Sprague-Dawley rats induced with STZ	25 mg/kg BW daily for 45 days; 50 and 100 mg/kg BW daily for 6 weeks	Decreased BW; Reduced TNF-α adipocyte gene and protein expression; Increased adipocyte and skeletal muscle GLUT4 gene and protein expression; Reduced serum glucose, insulin, TG, TC, FFA, LDL-C and VLDL-C levels; Increased serum HDL-C levels; Improved glucose tolerance; Reduced plasma, serum, liver and pancreatic TBARS and hydroperoxide levels; Increased SOD, CAT and GPx levels	[168,169]
	High-fat diet fed obese female ovariectomized C57BL/6 J mice	1% and 3% supplemented diet (wt/wt diet) for 5, 11 and 22 weeks	Decreased BW and calorie intake; Reduced ScWAT and intra-abdominal adiposity (pgWAT, mWAT, mammary WAT); Reduced leptin, *Il-6*, *Ccl2*, and *α-Sma* gene expression in pgWAT, ScWAT and mammary adipose tissue; Elevated locomotor activity; Reduced plasma, muscle and hepatic glucose, insulin, TC, TG, leptin and lipid levels; Reduced muscle diacylglycerol content and decreased HOMA-IR index; Decreased muscle and hepatic *Fasn*, *Scd1*, *Dgat2*, *Hsl* and *Acox1* gene expression; Increased hepatic *Srebf1*, *Cpt-1α*, *Pgc1α* and *Pck2* gene expression	[158,159,-160]
	High-fructose diet fed male Wistar rat	50 mg/kg BW daily for 6 weeks	Suppressed insulin resistance by decreasing plasma glucose, insulin, TG and FFA levels; Increased protein expression of SIRT1 and AMPK phosphorylation and upregulated *Pgc1α* gene expression in skeletal muscle; Increased protein expression of GLUT4 translocation in skeletal muscle; Increased hepatic eNOS protein expression; Reduced TBARS levels, lipid hydroperoxides and protein carbonyl content in plasma, liver and skeletal muscle; Increased SOD, CAT, GPx, GR, GST and GHS activities in the liver and skeletal muscle	[177,178,-179]
	High-fat and high-fructose diet fed male Sprague − Dawley rats	2.6 mmol/kg supplemented diet for 13 weeks	Decreased BW; Reduced vWAT, pWAT and adipocyte hypertrophy in eWAT; Decreased serum and hepatic LDL-C, TC, TG and FFA levels; Increased serum HDL-C levels; Reduced serum leptin, TNF-α and IL-6 levels; Decreased serum MDA content and increased total anti-oxidant capacity level in serum	[164]
	High-cholesterol diet fed male New Zealand White rabbits	0.05% supplemented diet for 8 weeks	Decreased fat content in the aorta; Decreased *Vcam-1* and *Mcp-1* gene expression in aorta; Reduced hepatic ACAT activity	[176]
Eriocitrin	High-fat and high-cholesterol diet fed male Sprague-Dawley rats	0.35% and 0.70% supplemented diet (g/g diet) for 21 days	Lowered serum TC, VLDL-C, LDL-C, TG, and phospholipid levels; Increased fecal bile acid excretion	[182]
	Diet-induced (overfed) obese zebra fish	32 mg/kg daily for 4 weeks	Decreased plasma TG levels and reduced hepatic lipid content; Increased hepatic mitochondrial β-oxidation and expression of genes involved in mitochondrial biogenesis including *Tfam*, *Nrf1*, *Cox4I1*, *Atp5j*; Increased expression of lipid metabolism genes including *Pparα*, *Acox1* and *Acadm*	[184]
Hesperidin and eriocitrin	High-fat diet fed male C57BL/6 J mice	100 (hesperidin) and 200 (eriocitrin) mg/kg BW daily for 4 weeks	Decreased serum glucose, TC, LDL-C, TBARS, IL-6, MCP-1 and Hs-CRP levels; Increased serum HDL-C and ABTS levels; Reduced hepatic fat accumulation; Decreased hepatic TBARS levels and reduced liver damage	[183]
Luteolin	High-fat diet fed male C57BL/6 mice	10 mg/kg BW daily for 20 weeks; 0.002% and 0.01% supplemented diet (g/g diet) for 10, 12 and 20 weeks	Decreased BW and increased energy expenditure; Reduced food intake; Reduced adipose tissue weights (eWAT, ScWAT and BAT) and decreased adipocyte hypertrophy in eWAT; Reduced adipose tissue inflammation, decreased M1 macrophage and mast cells infiltration in eWAT; Increased M2 macrophage infiltration in eWAT and enhanced eWAT angiogenesis; Decreased *F4/80*, *Mcp-1*, *Il-6*, *Tnf-α*, *Cd36*, *Plin2* and *mMCP-4* expression in eWAT; Increased AMPKα1 signaling and protein expression of AKT phosphorylation and GLUT4 translocation in eWAT; Stimulated thermogenic and beige cell markers (*Ucp1*, *Pgc1α*, *Pparα*, *Cidea*, *Elovl3*, *Sirt1*, *Tmem26*, *Cd137* and *Cited1* gene expression) in BAT and ScWAT; Increased protein expression of UCP1, AMPKα and ACC phosphorylation in BAT and ScWAT; Improved glucose intolerance by decreasing plasma and serum glucose and insulin levels; Induced insulin sensitivity and reduced HOMA-IR index; Reduced plasma and serum TG, TC, leptin, resistin, MCP-1, IL-6 and TNF-α levels; Increased plasma and serum adiponectin levels; Decreased TNF-α levels and increased protein expression of SOD1 and miR-214-3p expression in mesenteric arteries; Decreased TBARS, TNF-α and IL-1β levels in brain; Decreased *Tnf-α* and *Il-1β* gene expression in brain and reduced NF-κB protein expression in brain; Increased SOD and GSH levels in brain	[206,205,-204,211,-318]
	High-fat diet fed male C57BL/6 J and C57BL/6 N mice	0.005% supplemented diet (wt/wt) for 16 weeks; 50 and 250 ppm supplemented diet (g/kg diet) for 8 weeks; 0.6% and 1.5% supplemented diet (wt/wt) for 3 and 57 days	Decreased BW gain and reduced adipose tissue weights (eWAT, pWAT, rWAT, mWAT, vWAT, ScWAT and iWAT); Reduced food efficiency ratio; Increased *Acc*, *Srebp1*, *Srebp2*, *Cpt-1*, *Cpt-2*, *Ucp-1*, *Pgc1β*, *Cd36* and *Lpl* gene expression, and increased SREBP1 and PPARγ protein expression in eWAT; Reduced macrophage infiltration and fibrosis in eWAT and liver; Decreased *Cd68*, *Ccl2*, *F4/80* and *Saa3* gene expression in eWAT and modulated TLR signaling pathway; Decreased plasma and serum TC, TG, FFA, VLDL-C, LDL-C, Apo B48 and Apo B100 levels; Improved glucose tolerance and HOMA-IR index by decreasing glucose and insulin levels; Decreased hepatic steatosis and reduced liver TG, TC and FFA content; Reduced plasma leptin, resistin, TNF-α, MCP-1, IL-6, IL-1β, sCD163, MIP-1β, PAI-1 and adipsin levels; Increased plasma adiponectin levels; Decreased hepatic enzyme activity and protein expression of G6PDH, CIDEA, PPARγ, ACC, SREBP1, SREBP2, FASN, HMGCR, ACAT, PAP, CPT, Apo B, HNF1α, HNF4α, MTP, PEPCK and G6Pase; Increased hepatic enzyme activity of CPT and upregulated hepatic gene expression of *Pparα*, *Cidea*, *Pgc1α* and *Pgc1β*; Increased glucokinase enzyme activity and the protein expression of AMPK phosphorylation in the liver; Reduced mitochondrial and cytosol H_2O_2, TBARS and glycogen content in the liver; Increased hepatic SOD, CAT and GPx activities; Lowered hepatic lipotoxicity; Increased fecal cholesterol, TG and FFA content	[207,208,-209,212,-213]

(*continued on next page*)

Table 3 (*continued*)

Compound	Experimental Model	Dose and Treatment Period	Experimental Outcomes and Proposed Mechanism	References
	Western diet fed male *Ldlr*$^{-/-}$ C57BL/6 mice	100 mg/kg diet for 14 weeks	Reduced aortic lipid accumulation; Decreased plasma TC, TG and LDL levels; Reduced aortic *Cd68*, *Mcp-1*, *Il-6* and *Tnf-α* expression	[319]
	C57BL/KsJ- *db/db* (Lepr$^{db/db}$) male mice	20 and 100 mg/kg BW daily for 8 weeks	Decreased BW gain, reduced plasma and hepatic TG levels, decreased hepatic lipid accumulation, increased hepatic glycogen content and improved glucose tolerance; Decreased hepatic LXRα, LXRβ, SREPB1c, FASN, SCD1, ACC1 and GPAM gene and protein expression	[210]

Abbreviations: α-KGDH, alpha-ketoglutarate dehydrogenase; α-SMA, alpha smooth muscle actin; ABCA1, ATP binding cassette subfamily A member 1; ABCG1, ATP binding cassette subfamily G member 1; ABCG8, ATP binding cassette subfamily G member 8; ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); ACADM, acyl coenzyme A dehydrogenase; ACAT, acetyl coenzyme A: cholesterol acyltransferase; ACC, acetyl coenzyme A carboxylase; ACCα, acetyl coenzyme A carboxylase alpha; ACO, acyl coenzyme oA oxidase; ACOX1, acyl coenzyme A oxidase 1; AGE, advanced glycation end products; AKT, protein kinase B; AMPK, 5′ AMP-activated protein kinase; AMPK1α, 5′ AMP-activated protein kinase alpha 1; Apo B, apolipoprotein B; Apo B100, apolipoprotein B100; Apo B48, apolipoprotein B48; ATGL, adipose tissue triglyceride lipase; ATP5J, ATP synthase peripheral stalk subunit F6; ATP5g1, ATP synthase lipid-binding protein mitochondrial; BAT, brown adipose tissue; BW, body weight; CAT, catalase; CCL2, C-C motif chemokine ligand 2; CCL3, C-C motif chemokine ligand 3; CD137, tumor necrosis factor receptor superfamily member 9; CD36, cluster of differentiation 36; CD68, cluster of differentiation 68; CE, cholesterol esters; ChREBP, carbohydrate-responsive element-binding protein; CIDEA, cell death-inducing DNA fragmentation factor α-like effector A; CITED1, Cbp/p300-interacting transactivator 1; COXI, cytochrome c oxidase I; COXIV, cytochrome c oxidase subunit 4 isoform 1; COX4I1, cytochrome c oxidase subunit 4I1; COX6B1, cytochrome c oxidase subunit 6B1; CPT-1, carnitine palmitoyltransferase 1; CPT-2, carnitine palmitoyltransferase 2; Cyt-c, cytochrome 2; CYP2b9, cytochrome P450 family 2 subfamily b, polypeptide 9; CYP3A4, cytochrome P450 family 3 subfamily A member 4; CYP7A1, cytochrome P450 family 7 subfamily A member 1; DGAT, diglyceride acyltransferase; DGAT2, diglyceride acyltransferase 2; DHTKD1, dehydrogenase E1 and transketolase domain containing 1; ELOVL3, ELOVL fatty acid elongase 3; EMR1, EGF-like module containing, mucin-like, hormone receptor-Like 1; eNOS, endothelial nitric oxide synthase; ER, endoplasmic reticulum; ERRα, estrogen-related receptor alpha; eWAT, epididymal white adipose tissue; F4/80, macrophage-specific adhesion-G protein-coupled receptors E1; FA, fatty acid; FASN, fatty acid synthase; FFA, free fatty acids; FGF21, fibroblast growth factor 21; G6Pase, glucose 6-phosphatase; G6PDH, glucose-6-phosphate dehydrogenase; GLUT4, glucose transporter 4; GPAM, glycerol-3-phosphate acyltransferase 1 mitochondrial; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GST, glutathione S-transferase; H_2H_2, hydrogen peroxide; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment insulin resistance; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HMG-CoA, 3-hydrox-y 3-methylglutaryl-coenzyme A; HNF1α, hepatocyte nuclear factor 1 alpha; HNF4α, hepatocyte nuclear factor 4 alpha; Hs-CRP, high-sensitivity C-reactive protein; HSL, hormone sensitive lipase; iBAT, interscapular brown adipose tissue; ICR, imprinting control region; IDH, isocitrate dehydrogenase 1; IL-1β, interleukin 1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; iWAT, inguinal white adipose tissue; JNK, c-Jun N-terminal kinase; LDL-C, low-density lipoprotein cholesterol; LEPR, leptin receptor; LKB1, liver kinase B1; LOOH, lipid hydroperoxide; LPO, lipid peroxide; LPL, lipoprotein lipase; LXRα, Liver X receptor alpha; LXRβ, Liver X receptor beta; Mac-2, macrophage marker 2; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; MIP-1β, macrophage inflammatory protein 1 beta; miR-214-3p, microRNA -214-3p; mMCP-4, mast cell protease 4; mtDNA, mitochondrial deoxyribonucleic acid; mTOR, mechanistic target of rapamycin; MTP, microsomal triglyceride transfer protein; mWAT, mesenteric white adipose tissue; NEFA, non-esterified fatty acids; NF-κB, nuclear factor kappa B; NO, nitric oxide; NRF1, nuclear respiratory factor 1; ox-LDL, oxidized low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; PAP, Phosphatidate phosphatase; PEPCK, phosphoenolpyruvate carboxykinase; PCK2, phosphoenolpyruvate carboxykinase 2; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGC1β, peroxisome proliferator-activated receptor gamma coactivator 1 beta; pgWAT, perigonadal white adipose tissue; PLIN2, perilipin 2; PNPLA2, patatin like phospholipase domain containing 2; PPARα, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; PON, paraoxonase; pWAT, perirenal white adipose tissue; pvWAT, perivascular adipose tissue; RBP4, retinol binding protein 4; RER, respiratory exchange ratio; ROS, reactive oxygen species; rWAT, retroperitoneum white adipose tissue; SAA, serum amyloid a; SCD1, stearoyl-CoA desaturase-1; sCD163, soluble CD antigen 163; ScWAT, subcutaneous white adipose tissue; SDHβ, succinate dehydrogenase beta; SIRT1, sirtuin-1; SOD, superoxide dismutase; SREBP1c, sterol regulatory element-binding protein 1c; SREBF1, sterol regulatory element-binding transcription factor 1; SREBF2, sterol regulatory element-binding transcription factor 2; STZ, streptozotocin; TBARS, thiobarbituric acid reactive substances; TC, total cholesterol; TCA, tricarboxylic acid; TFAM, transcription factor A mitochondrial; TG, triglycerides; TLR2, toll-like receptor 2; TNF-α, tumour necrosis factor alpha; TMEM26, transmembrane protein 26; UCP1, uncoupling protein 1; UCP2, uncoupling protein 2; UCP3, uncoupling protein 3; VCAM-1, vascular cell adhesion molecule-1; VLDL-C, very low-density lipoprotein cholesterol; vWAT, visceral white adipose tissue; wt, weight.

would release hesperetin [126]. The anti-obesity properties of hesperidin and hesperetin have been reported *in vitro* and *in vivo* [79,81,127–135]. In adipocyte *in vitro* models such as the 3T3-L1 pre-adipocytes and hMSCs (Table 2), hesperidin and hesperetin inhibited adipogenesis, decreased lipid and triglyceride accumulation, reduced oxidative stress, and stimulated lipolysis [81,127–131]. Furthermore, hesperetin was reported to stimulate cholecystokinin secretion, an appetite-regulating hormone, in enteroendocrine STC-1 cells [136]. Dietary supplementation or intragastric gavage with hesperidin (100–800 mg/kg daily for 5–12 weeks) exhibited anti-hyperlipidemic effects in high-cholesterol diet (HCD) fed rats, Lepr$^{db/db}$ and HFD fed low-density lipoprotein (LDL) receptor null (*Ldlr*$^{-/-}$) mice, by decreasing plasma and hepatic FFA, triglyceride and cholesterol levels (Table 3) [79,132,133]. Hesperidin further decreased perirenal adipose tissue weight and reduced hepatic steatosis by decreasing the activity of enzymes involved in cholesterol synthesis (Table 3) [79,132]. Using *Caenorhaditis elegans* as an *in vivo* model, Peng et al. [137] reported that hesperidin inhibits lipid accumulation by decreasing the expression of genes involved in lipid metabolism. Similarly, hesperetin was reported to reduce body weight gain and abdominal adipose tissue weight, and decrease serum leptin levels in HFD fed rodents (Table 3) [127,134,135].

Few studies evaluated the effects of hesperidin on obesity and associated metabolic disease in humans (Table 4). Administration of a water-soluble hesperidin derivative, glucosyl hesperidin (G-hesperidin), reduced serum triglyceride levels and improved very low-density lipoprotein cholesterol (VLDL-C) metabolic abnormality in hypertriglyceridemic patients [138]. A combination of G-hesperidin and caffeine (PubChem CID: 2519) decreased abdominal fat area and BMI in healthy, moderately obese subjects [139]. In contrast to these studies, consumption of pure hesperidin did not reduce serum TC and LDL-C levels in moderately hypercholesterolemic subjects (Table 4) [140]. These studies suggest that poor bioavailabity of hesperidin compared to its derivatives [141] may contribute to its limited bioactivity. Co-treatment of hesperetin with trans-resveratrol (PubChem CID: 445154), compared to the respective compounds, improved metabolic and vascular health in overweight and obese subjects (Table 4) [142], suggesting that the combined effects of these compounds increase their

Table 4
Summary of clinical human studies reporting on the effects of mangiferin, hesperidin and hesperetin on obesity and associated comorbidities, and their mechanism of activity.

Compound	Subjects	Dose Used and Intervention Period	Outcomes and Mode of Activity	Reference
Mangiferin	Overweight patients (men and women) with hyperlipidemia (serum TC ≥ 5.2 mmol/l and TG ≥ 1.7 mmol/l)	150 mg/day for 12 weeks	Decreased serum TG and FFA levels; Reduced HOMA-IR index; Increased serum HDL-C, β-hydroxybutyrate, L-carnitine and acetoacetate levels; Increased serum LPL activity	[106]
Hesperidin	Hyperlipidemic men classified into normal (TC < 5.9 mmol/l, TG < 1.7 mmol/l), high-TC (TC > 5.9 mmol/l, TG < 1.7 mmol/l) and high-TG (TG > 1.7 mmol/l) groups	100 and 500 mg/day for 6 weeks	Reduced TG, apo C-II and apo E levels in the high-TG group; Increased LDL-C/apo B ratio in the high-TG group	[320]
	Hypertriglyceridemic men classified into high TG (TG > 1.7 mmol/l), borderline TG (TG 1.2 – 1.7 mmol/l) and normal TG (TG < 1.2 mmol/l) groups	500 mg/day for 24 weeks	Decreased serum TG, RLP-C, apo B, apo C-II, apo C-III and apo E levels in the high-TG group; Repaired VLDL-C metabolic abnormality; Suppressed LDL-C formation	[138]
	Moderately hypercholesterolemic men and women with BMI (20 – 30 kg/m^2), serum TC (5.0 – 8.0 mmol/l) and serum TG < 4.0 mmol/l	800 mg/day for 4 weeks	No effect on serum TC, LDL-C, HDL-C and TG concentrations	[140]
	Healthy men and women with moderately high BMI (24 – 30 kg/m^2) and serum TG (1.1 – 2.8 mmol/l)	500 mg (G-hesperidin) with or without 25, 50, 75 mg caffeine daily for 12 weeks	Decreased abdominal and subcutaneous fat area; Reduced body weight and BMI	[139]
	Healthy overweight men	292 mg hesperidin or 500 ml orange juice with 292 mg naturally containing hesperidin daily for 4 weeks	Altered leukocyte gene expression to an anti-inflammatory and anti-atherogenic profile; Improved diastolic blood pressure	[321,322]
	Patients (men and women) with metabolic syndrome[a]	500 mg/day for 3 weeks	Reduced circulating serum levels of pro-inflammatory Hs-CRP, SAA protein and sE-selectin markers; Improved endothelial function	[323]
Hesperetin	Overweight and obese men and women	Coformulation: 90 mg (tRES) and 120 mg (HESP) daily for 8 weeks	Increased *GLO1* gene expression in PBMC and improved vascular function; Decreased fasting and postprandial plasma glucose; Decreased *CCL2*, *HIF1A*, *IL-8*, *PTGS2*, *FTH1*, *RAGE*, *KEAP1* and *TNFA* gene expression in PBMC	[142]

Abbreviations: apo B, apolipoprotein B; apo C-II, apolipoprotein C2; apo C-III, apolipoprotein C3; apo E, apolipoprotein E; BMI, body mass index; *CCL2*, C-C motif chemokine ligand 2; FFA, free fatty acids; *FTH1*, ferritin heavy chain 1; *GLO1*, Glyoxalase I; HDL-C, high-density lipoprotein cholesterol; HESP, hesperetin; *HIF1A*, hypoxia inducible factor 1 subunit alpha; HOMA-IR, homeostatic model assessment of insulin resistance; Hs-CRP, high-sensitivity C-reactive protein; *IL-8*, interleukin 8; *KEAP1*, kelch-like ECH-associated protein 1; LDL-C, low-density lipoprotein; LPL, lipoprotein lipase; PBMC, peripheral blood mononuclear cell; *PTGS2*, prostaglandin-endoperoxide synthase 2; *RAGE*, receptor for advanced glycation end products; RLP-C, remnant-like particle cholesterol; SAA, Serum amyloid A; sE-selectin, soluble adhesion molecules; TC, total cholesterol; TG, triglyceride; *TNFA*, tumour necrosis factor alpha; tRES, trans-resveratrol; VLDL-C, very low-density lipoprotein cholesterol.

[a] According to the National Cholesterol Education Program Adult Treatment Panel III criteria.

bioactivity.

Naringenin (4′,5,7-trihydroxyflavanone) (PubChem CID: 932), an aglycone flavanone found abundant in citrus such as grapefruit, has been detected in honeybush extracts such as *C. genistoides* [143]. It is, however, not present in detectable quantities in hot water infusions of "fermented" *C. genistoides* and others [11,83]. Beelders et al. showed the presence of naringenin derivatives in *C. genistoides* [120], later identified by Danton et al. [122], as 5-[α-L-rhamnopyranosyl-(1→2)-β-D-glucopyranosyloxy] naringenin diastereomers with the 2*S*-diastereomer predominant, and the 2*R*-diastereomer formed through epimerization during heating and the high temperature oxidation process ("fermentation") of the plant material [120,122]. Similar to hesperidin, the release of naringenin is to be expected in the gut [144–146]. Using *in vitro* adipocyte models and *in vivo* animal models of obesity and associated metabolic complications, several studies demonstrated the anti-obesity and anti-inflammatory properties of naringenin (Tables 2 and 3). Naringenin was shown to inhibit adipocyte differentiation [127,147] and TNF-α-induced lipolysis in 3T3-L1 adipocytes and mouse primary adipocytes [148]. Other *in vitro* studies (Table 2) reported that naringenin inhibits TNF-α-stimulated FFA and monocyte chemoattractant protein 1 (MCP-1) secretion in adipocytes co-cultured with macrophages, 3T3-L1 adipocytes and mouse primary adipocytes [148–152]. Naringenin also promoted thermogenic gene expression in human white adipose tissue [153]. In diet-induced and genetically obese rodents, naringenin ameliorated obesity by reducing body weight, decreasing visceral and subcutaneous adiposity, increasing energy expenditure and attenuating adipose tissue inflammation (Table 3) [127,151,152,154–164]. Naringenin also improved hyperlipidemia by decreasing circulatory and hepatic lipids, inhibiting fatty acid synthesis and increasing fatty acid oxidation in heart, muscle and hepatic tissues (Table 3) [127,157,165–171]. In diet-induced obese rodents, naringenin decreased hepatic steatosis, attenuated systematic and hepatic inflammation, reduced oxidative stress, prevented atherosclerosis and improved insulin sensitivity (Table 3) [157,166,168,169,172–179]. Like naringenin, naringin (PubChem CID: 442428), one of its glycosidic form (not detected in infusions and aqueous extracts of *Cyclopia* spp.), has been shown to ameliorate obesity and obesity-related metabolic disturbances [180].

Eriocitrin (eriodictyol 7-*O*-rutinoside) (PubChem CID: 83489) has been detected in several *Cyclopia* extracts [83,120,121,181]. To date, neither *in vitro* nor *in vivo* studies reported on the anti-obesity properties of eriocitrin in adipose tissue, however, studies have shown that this flavonoid ameliorates obesity in other tissues and in the circulation (Table 3). In particular, treatment with eriocitrin lowered serum lipid profile levels in HFD and HCD fed rats [182], and suppressed HFD-induced systemic inflammation in mice [183]. Similarly, eriocitrin reduced plasma triglyceride levels and hepatic steatosis in diet-induced obese zebrafish, and this was mediated by increased mitochondrial beta (β)-oxidation (Table 3) [184]. Correspondingly, eriocitrin is expected to be hydrolyzed to eriodictyol (PubChem CID: 440735), its aglycone, by

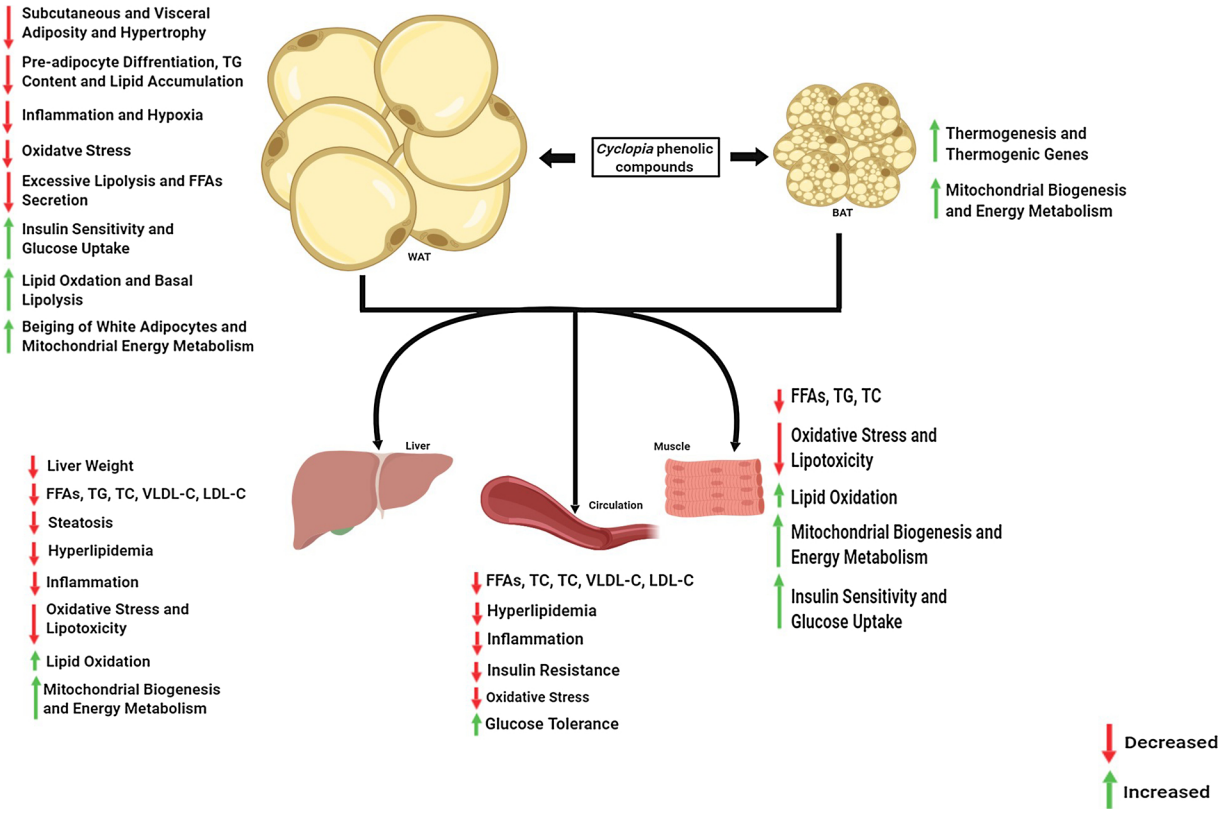

Fig. 2. Summary of the effects of *Cyclopia* phenolic compounds on obesity and associated metabolic disease, and the major tissues modulated by *Cyclopia* phenolic compounds. In this study, we speculate that the phenolic compounds of *Cyclopia* target BAT, increasing thermogenesis, mitochondrial energetics and energy expenditure, and target WAT, preventing adipose tissue dysfunction by reducing adipocyte hypertrophy, inflammation, hypoxia, oxidative stress and excessive lipolysis, and enhancing insulin sensitivity and the browning of white adipocytes. The anti-obesity effects of the phenolic compounds of *Cyclopia* in BAT and WAT, ameliorates obesity-associated complications in the liver by reducing hyperlipidemia and cholesterol metabolism, steatosis and lipid content, inflammation, lipotoxicity and oxidative stress, and inducing lipid oxidation, mitochondrial biogenesis and energy metabolism. In the circulation, the phenolic compounds of *Cyclopia* reduce hyperlipidemia, lipid profile, inflammation, oxidative stress and insulin resistance, and improve glucose tolerance. In the muscle, the phenolic compounds of *Cyclopia* decrease lipid content, oxidative stress and lipotoxicity, and induce lipid oxidation, mitochondrial biogenesis and bioenergetics, and stimulate insulin sensitivity and glucose uptake.

Figure abbreviations: BAT, brown adipose tissue; FFAs, free fatty acids; LDL-C, low-density lipoprotein cholesterol, TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol; WAT, white adipose tissue.

intestinal bacteria [144,185]. Eriodictyol has been shown to possess anti-diabetic, anti-inflammatory and anti-obesity properties [183,186–190]. In HFD-fed obese mice, eriodictyol alleviated obesity by reducing fat deposition and decreasing lipogenesis-related gene expression in white adipose tissue, thus protecting against obesity-associated metabolic complications by reducing hepatic steatosis, decreasing plasma and hepatic triglyceride, TC and FFA levels, improving insulin sensitivity, and protecting against systematic inflammation and oxidative stress [183,189]. Our literature search did not retrieve any clinical studies reporting on the anti-obesity effects of naringenin, eriocitrin and eriodictyol in humans.

More recently, we identified the relative abundance of neoponcirin (isosakuranetin-7-*O*-rutinoside) (PubChem CID: 16760075), also known as didymin, in *C. intermedia* [16], however, the anti-obesity potential of this flavanone or its aglycone, isosakuranetin (PubChem CID: 160481), has not been reported to date, although studies have shown that didymin prevents hyperglycemia-induced endothelial dysfunction and inflammation, and attenuates vascular endothelial growth factor (VEGF)-induced angiogenesis [191,192], while stimulating glucose uptake and reducing hepatic glucose production in insulin resistant HepG2 cells [193], demonstrating its cardioprotective and anti-diabetic effects.

5.2.2. Flavones

Luteolin (3′,4′,5,7-tetrahydroxyflavone) (PubChem CID: 5280445), characterized by hydroxyl moieties at positions 5, 7, 3′, and 4′ and a 2–3 carbon double bond [194], has been detected in relatively low concentrations in *Cyclopia* extracts such as *C. intermedia* and *C. subternata* [16,117–119]. Scolymoside (PubChem CID: 5282152), the 7-*O*-neohesperidoside of luteolin, is one of the major compounds in *C. subternata* extracts [16,181]. Numerous *in vitro* studies have shown that luteolin protects against obesity by decreasing lipid accumulation and triglyceride content in 3T3-L1 adipocytes (Table 2) [131,195–200]. Luteolin also suppressed inflammation in adipocytes co-cultured with macrophages, and in adipocytes stimulated with a macrophage-conditioned media or a combination of TNF-α, LPS and interferon gamma (IFN-γ) [201–203]. In brown and subcutaneous primary adipocytes, luteolin increased the expression of thermogenic and beige cell gene markers and activated the 5′ AMP-activated protein kinase/peroxisome proliferator-activated receptor gamma coactivator 1-alpha (AMPK/PGC1α) signaling (Table 2) [204]. In HFD-induced obese mice, dietary supplementation with luteolin decreased body weight, reduced adipocyte hypertrophy in epididymal adipose tissue, increased energy expenditure and induced thermogenesis, activated browning in subcutaneous adipose tissue, suppressed adipose tissue inflammation, and stimulated insulin sensitivity by activating AMPK-alpha 1 (AMPKα1) signaling (Table 3) [204–207]. These studies suggest that AMPK signaling might be an important target for luteolin in adipose tissues. Further *in vivo* studies (Table 3) reported that luteolin alleviates obesity-associated metabolic disorders such as hyperlipidemia, hepatic steatosis and cardiovascular dysfunction in HFD fed and Lepr$^{db/db}$ mice [208–213]. Our literature search could not identify any studies reporting on the anti-obesity potential of luteolin in humans. The anti-obesity properties of scolymoside have not been reported yet, although this flavone was shown to inhibit high-glucose, LPS, polyphosphate and transforming growth factor β-induced protein (TGFBIp)-induced vascular inflammation [214–217]. Vicenin-2 (apigenin 6,8-di-*C*-β-D-glucopyranoside) (PubChem CID: 442664) is a *C*-glycosyl flavone detected in *C. subternata*, *C. genistoides*, *C. longifolia*, *C. maculata* and *C. intermedia* extracts [16,83,120,181]. Although its anti-obesity properties have not been reported, vicenin-2 has anti-diabetic [218,219] and anti-inflammatory [214–217] effects.

5.2.3. Dihydrochalcones

The two dihydrochalcones, phloretin-3′,5′-di-*C*-β-D-glucoside and 3-hydroxy-phloretin-3′,5′-di-*C*-hexoside, are present in *C. subternata*, *C. maculata* and *C. genistoides* [11,83,120,121,124,181]. Our literature search did not retrieve any studies reporting on the anti-obesity properties of these *Cyclopia* dihydrochalcones, although these compounds have been identified in high concentration in extracts of some *Cyclopia* spp. Interestingly, the dihydrochalcones are very similar to aspalathin (PubChem CID: 16752601), a *C*-glucosyl dihydrochalcone with modulatory effects against insulin resistance [220,221]. Aspalathin, unique to *Aspalathus* species, another endemic South African plant genus, more commonly known for rooibos *(Aspalathus linearis*), has been shown to improve lipid and glucose metabolism in insulin resistant adipocytes [220]. The anti-obesity properties of other dihydrochalcones not present in *Cyclopia*, such as phloridzin (phloretin-2′-β-D-glucopyranoside) (PubChem CID: 6072) and its aglycone, phloretin [222] (PubChem CID: 4788), are extensively reported [223–229]. In HFD-fed mice, phloridzin decreased body weight and fat mass by alleviating lipid metabolism and glucose homeostasis, increasing brown adipose tissue activity, and upregulating the expression of proteins involved in brown adipose tissue thermogenesis [227], while both phloretin and phloridzin prevented obesity, attenuated adipose tissue inflammation and fibrosis, and reduced insulin resistance and hepatic steatosis in HFD-induced obese mice [223,225,229]. Phloretin and phloridzin also decreased lipid accumulation by stimulating lipolysis in 3T3-L1 adipocytes, and suppressed inflammation by reducing nitrite and pro-inflammatory cytokine secretion levels in TNF-α-induced 3T3-L1 adipocytes, in 3T3-L1 adipocytes co-cultured with macrophages and in macrophages induced with adipocyte-conditioned media [226]. Thus, the anti-obesity potential of *Cyclopia* dihydrochalcones warrants further investigation.

5.3. Benzophenones

Benzophenones are a class of natural compounds abundant in plants such as the *Clusiaceae* family [230], but recently, the *C*-glucosyl benzophenones, 3-β-D-glucopyranosyliriflophenone, 3-β-D-glucopyranosyl-4-β-D-glucopyranosyloxyiriflophenone and 3-β-D-glucopyranosylmaclurin have been detected in several *Cyclopia* extracts [83,120,124,125,231–234]. *In vitro* studies reporting on the anti-obesity potential of *Cyclopia* benzophenones are limited (Table 2), while there is currently no *in vivo* animal and human studies that have reported on the anti-obesity potential of these benzophenones. Zhang et al. [235–237] reported that 3-β-D-glucopyranosyliriflophenone and 3-β-D-glucopyranosylmaclurin decreased lipid accumulation, triglyceride content and FFA accumulation in 3T3-L1 adipocytes (Table 2). In addition, 3-β-D-glucopyranosyl-4-β-D-glucopyranosyloxyiriflophenone and 3-β-D-glucopyranosyliriflophenone marginally increased glucose uptake in 3T3-L1 adipocytes and C3A hepatocytes [231], while 3-β-D-glucopyranosyliriflophenone lowered fasting blood glucose levels in diabetic mice and enhanced glucose uptake in cultured adipocytes derived from white epididymal fat pads [238], demonstrating their anti-diabetic potential.

6. *Cyclopia* as a source of phenolic compounds exhibiting potential anti-obesity bioactivity

The studies included in this review suggest that the anti-obesity properties of *Cyclopia* extracts may be attributed to their phenolic constituents, but whether a single compound or combinatorial effects as a result of the complex mixture of polyphenols, or other extract constituents such as pinitol (PubChem CID: 164619), could be responsible for the anti-obesity potential of *Cyclopia*, are still to be elucidated. Pinitol is a cyclitol compound, occurring in *Cyclopia* spp. [117,119]. This compound showed anti-inflammatory effects in human obesity by reducing the circulating levels of IL-6 and TNF-α, increasing sirtuin-1 (SIRT1) expression in peripheral blood mononuclear cells, and reducing the expression of IL-6, TNF-α, and the endoplasmic reticulum stress markers in subcutaneous white adipose tissue [239]. Using high performance counter-current chromatography (HPCCC) to separate the

crude polyphenol-enriched fraction (CPEF) of *C. intermedia* into four major sub-fractions, we demonstrated that fractionation does not enhance activity within a single fraction, but rather that all the sub-fractions exhibited anti-obesity effects, suggesting that the anti-obesity potential of *C. intermedia* is attributed to more than one phenolic compound [17]. Furthermore, the anti-obesity effects of the CPEF of *C. intermedia* were greater compared to the HPCCC sub-fractions, suggesting potential combinatorial effects between phenolic constituents [16,17].

Generally, polyphenols are known to have poor bioavailability, due to their low absorption in the human gastrointestinal (GI) tract, rapid biotransformation in the gut and liver and excretion from the body [240]. Several factors, including the chemical structure, molecular weight, low stability or the gastrointestinal environment contribute to poor bioavailabity of phenolic compounds [241]. For example, mangiferin has low bioavailabity, due to its sugar glucoside that is directly attached to the aglycone by the C—C bond, making it more resistant to acid and enzyme hydrolysis [107,242–245]. Other studies reported increased bioavailability of mangiferin, when administered with a herbal formulation [246] or with absorption enhancers such as sodium deoxycholate (PubChem CID: 23668196) and Carbopol 974P (PubChem CID: 8314) [247]. Similarly, studies have shown that hesperidin is poorly absorbed in its glycoside form due to the attached rutinoside moiety that requires hydrolysis, most likely by bacterial intestinal enzymes, before being absorbed in its aglycone form (hesperetin) and further metabolized in the intestinal epithelium and liver [248,249]. Poor bioavailability of hesperidin is also attributed to its low water solubility, hence a water-soluble derivative of hesperidin, G-hesperidin, with similar metabolic profile as hesperidin, was absorbed more rapidly and efficiently than hesperidin in rats [141]. Similarly, α-monoglucosyl hesperidin increased energy expenditure by stimulating the formation of brown-like adipocytes and inducing thermogenesis in mouse inguinal white adipose tissue (iWAT), while hesperidin was not effective [250]. In line with this, the metabolites of mangiferin and hesperidin, norathyriol and hesperetin, were absorbed from the gastrointestinal tract of pigs after an oral administration of a *C. genistoides* extract [251], and high hesperetin levels were detected in the liver and aorta of rats after consuming a hesperetin-containing diet for 4 weeks, suggesting that the aorta is one of the main target tissues of hesperetin for exerting its functions [252]. The solubility and bioavailability of naringenin is also reported to be low, and this is attributed to its largely hydrophobic ring structure [253]. Co-treatment with the excipient, hydroxypropyl-β-cyclodextrin (PubChem CID: 14049689), enhanced the solubility and bioavailability of naringenin and ameliorated dyslipidemia and diabetes in rats [254]. Naringenin was detected in human plasma after consumption of a meal containing cooked tomato paste [255], suggesting its bioavailability when consuming tomato-containing food. Thus, further studies into the bioavailability and mechanism of action of *Cyclopia* phenolic compounds are essential for developing anti-obesity agents that efficiently target and reach the site of action.

To date, the human studies examining the effects of *Cyclopia* extracts focused on the skin [256,257] and no other clinical or human studies, including an investigation of their anti-obesity potential, have been reported thus far. There are also no significant side effects reported for honeybush tea consumption by humans [258]. The widespread use of herbal medicines and natural compounds, especially in quantities much higher than normally consumed through the diet, have led to increasing, but valid concerns about their safety and toxicity in view of adverse biological and hepatotoxic effects of some products [259–262]. The information regarding the safety and toxicity of honeybush tea consumption, either as herbal tea or extract containing high levels of specific compounds, is very limited. A pre-clinical study by van der Merwe and colleagues [263] assessed the possible hepatoxicity and oxidative effects of polyphenol-enriched extracts of *C. genistoides* and *C. subternata* following short-term (28 days) and sub-chronic (90 days) dietary treatment of Fischer 344 rats. The authors reported that although these extracts exhibited limited adverse effects, they altered the expression of anti-oxidant defense and oxidative stress-related genes in the liver of rats, suggesting that dose and duration of exposure to the extracts should be monitored carefully [263]. Similarly, treatment of Fischer 344 rats with aqueous extracts prepared from fermented and unfermented *C. intermedia* had no significant effect on the activities of the liver function enzymes, aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) [264]. Further studies are required to evaluate the potential adverse effects of honeybush tea consumption, particularly its hepatoxic effects.

Cyclopia extracts contain a complex mixture with more than one active compound, thus increasing the possibility of herb-drug interactions, especially in patients taking chronic medications [265]. Herb-drug interactions can adversely affect drug metabolism, by either decreasing or increasing the concentration of a drug in a specific tissue, consequently inducing toxicity or reducing the efficacy of the drug treatment. Currently there are no studies reporting on any herb-drug interactions between *Cyclopia* extracts and the conventional drugs, although the phenolic compounds of *Cyclopia* have been reported to modulate drug metabolizing enzymes or interact with conventional drugs. The flavonoids, luteolin and naringenin, inhibit the activity of cytochrome P450 family 3 subfamily A member 4 (CYP3A4) [266–268], the main enzyme involved drug metabolism in the liver and gut [269]. An *in vivo* pharmacodynamic study showed that naringenin interferes with the anti-diabetic actions of pioglitazone (PubChem CID: 4829) [270], while the anti-diabetic activity of mangiferin was improved in combination with the hypoglycemic drugs, metformin (PubChem CID: 4091) and gliclazide (PubChem CID: 3475) [271]. Furthermore, hesperidin was responsible for the decreased intestinal absorption of celiprolol (beta-blocker) (PubChem CID: 42373), an antihypertensive drug, in rats [272].

7. Summary and conclusions

In the current paper, we systematically reviewed studies reporting on the anti-obesity properties of *Cyclopia* extracts and their major phenolic compounds, classified as xanthones, flavonoids and benzophenones. Extracts from *C. maculata*, *C. intermedia* and *C. subternata* were reported to inhibit adipogenesis, decrease lipid accumulation, stimulate lipolysis, and decrease body weight gain in Lepr$^{db/db}$ mice, however, their mechanism of action is not yet fully elucidated. The anti-obesity properties of several *Cyclopia* phenolic compounds, common to other plants, are widely reported. These compounds improve lipid metabolism, induce thermogenesis, ameliorate oxidative stress, and reduce insulin resistance and inflammation *in vitro*, in adipocyte models (Fig. 2). In *in vivo* models, these compounds were shown to reduce obesity by decreasing body weight and adiposity, increasing energy expenditure, and promoting satiety (Fig. 2). Furthermore, they attenuate obesity-associated metabolic complications such as hyperlipidemia, hepatic steatosis, insulin resistance and cardiometabolic disorders in peripheral tissues (Fig. 2). Clinical studies reporting on the anti-obesity potential of *Cyclopia* phenolic compounds in humans are limited, and only mangiferin, hesperidin and hesperetin were tested in human studies, showing that they decreased body weight and adiposity, reduced inflammation and blood glucose levels, and improved hyperlipidemia and vascular function (Fig. 2). However, these studies were either contradictory, or the phenolic compounds were used in combination with other compounds, or a modified soluble form or derivative of the compounds were used. Additional translational studies from animals to humans are needed to further confirm the anti-obesity benefits of *Cyclopia* and its phenolic compounds. Our literature search did not retrieve any studies reporting on the anti-obesity properties of the dihydrochalcones, phloretin-3′,5′-di-*C*-β-D-glucoside and 3-hydroxyphloretin-3′,5′-di-*C*-hexoside, although these compounds have been identified in substantial quantities in extracts of some *Cyclopia* spp. The xanthone, isomangiferin, the flavanone, neoponcirin and the flavones,

scolymoside and vicenin-2, were reported to only ameliorate obesity-associated metabolic conditions. Furthermore, norathyriol, hesperetin, eriodictyol and naringenin, aglycone metabolites of mangiferin, hesperidin, eriocitrin and naringenin glycosides, respectively, also exerted anti-obesity activities *in vitro* and *in vivo*. In conclusion, this review demonstrates that *Cyclopia* is a potential source of anti-obesity compounds with adipose tissue as the potential therapeutic target of these compounds, thus providing motivation for further studies to elucidate mechanisms and underscore the development of honeybush-derived anti-obesity nutraceuticals.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by the South African Medical Research Council Self-Initiated Research (SAMRC-SIR) grant (BU 23143, CJ Malherbe), baseline funding from the Biomedical Research and Innovation Platform of the SAMRC (C Pheiffer), and the South African National Research Foundation (Grant No. 113459) for a grant-holder linked bursary awarded to Mokadi Mamushi.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopha.2019.109439.

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